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THE

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SEPTEMBER, 1931

ORIGINAL ARTICLES.

DIABETES MELLITUS AND ITS COMPLICATIONS.

AN ANALYSIS OF 827 CASES.

By Francis D. Murphy, M.S., M.D.,

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There are few diseases more commonly attended by complications than diabetes mellitus. The nature of this disturbance is such that the patient is predisposed not only to a variety of infections but to arteriosclerosis as well. An analysis of a large group of unselected cases of diabetes reveals in an impressive manner how serious are the complications of diabetes. The object of this study is to determine what diseases most commonly are associated with diabetes, and in what manner this association affects diabetics. For this purpose the records of 827 diabetics treated at the Milwaukee County Hospital from January 1, 1922, to January 1, 1930, were analyzed. This series is not made up of cases selected for hospital care on the basis of complications. The cases in this report represent a fair cross-section of all indigent diabetics in the community.

Table 1.—Cases of Diabetes Mellitus at Milwaukee County Hospital from 1922 to 1930 (827 Cases).

	No. of cases.	Per cent total cases.	Improved.		Unimproved.		Died.	
			No.	Per cent.	No.	Per cent.	No.	Per cent.
Total cases	827							
Without complications	146	17.63	142	97.26	3	2.05	1	0.69
With complications	681	82.37	428	64.22	14	2.05	239	35.18

TABLE 2.—SUMMARY OF THE VARIOUS COMPLICATIONS OF DIABETES MELLITUS IN THIS SERIES WITH AGE AND SEX INCIDENCE.

	No. of cases.	Per cent diabetic cases (No. 827).	Improved.		Unimproved.		Died.		Average age of males.	No. of males.	Average age of females.	No. of females.
			No.	Per cent.	No.	Per cent.	No.	Per cent.				
1. *a*. Primary coma	20	2.41	18	90.0	0	0	2	10.0	47	13	24	7
b. Secondary coma	13	1.57	3	23.0	0	0	10	76.9	47	7	32	6
Total coma (*a* + *b*)	33	3.99	21	63.6	0	0	12	36.3	47	20	28	13
2. Cardiorenal vascular disease, total	273	33.01	136	49.8	7	2.5	130	47.6	57	144	57	129
Cardiac	40	4.83	17	42.5	1	2.5	22	55.0	54	19	50	21
Nephritis	12	1.45	8	66.6	0	0	4	33.3	53	8	55	4
Apoplexy	25	3.02	8	32.0	0	0	17	68.0	61	10	59	15
Arteriosclerosis	124	15.00	68	54.8	4	3.2	52	41.9	60	69	55	61
Gangrene	72	8.70	35	48.6	2	2.7	35	48.6	57	38	62	34
3. Infections, total	86	10.39	58	67.4	0	0	28	32.5	50	42	44	44
Pneumonia	16	1.93	2	12.5	0	0	14	87.5	59	6	37	10
Influenza	1	0.12	1	100.0	0	0	0	0	62	1	0	0
Upper respiratory tract	13	1.57	11	84.6	0	0	2	15.3	40	7	57	6
Otitis media, mastoiditis	5	0.60	4	80.0	0	0	1	20.0	32	1	4	35
Gall bladder disease	5	0.60	5	100.0	0	0	0	0	0	0	50	5
Erysipelas	7	0.84	6	85.7	0	0	1	14.2	69	2	60	5
Abscess of skin	6	0.72	4	66.6	0	0	2	33.3	56	4	61	2
Abscess of other organs	12	1.45	9	75.0	0	0	3	25.0	50	10	55	2
Septicemia	3	0.36	0	0	0	0	3	100.0	59	1	48	2
Mononucleosis, infectious	1	0.12	1	100.0	0	0	0	0	0	0	11	1
Hepatitis, infectious	1	0.12	1	100.0	0	0	0	0	27	1	0	0
Glossitis	1	0.12	1	100.0	0	0	0	0	52	1	0	0
Infect. and inflam. genitourin. system	15	1.81	13	86.6	0	0	2	13.3	44	8	53	7
4. Tuberculosis, pulmonary	40	4.83	22	55.0	2	5.0	16	40.0	41	28	43	12

5. Carcinoma	8	0.96	2	25.0	2	25.0	4	50.0	59	4	51	4
6. Syphilis	31	3.74	22	70.9	0	0	9	29.0	54	19	49	12
7. Miscellaneous complications, total	210	25.39	169	80.4	3	1.4	38	18.0	47.5	124	54	86
Alcoholism	3	0.36	1	33.3	0	0	2	66.6	49	2	43	1
Anemia, pernicious	3	0.36	3	100.0	0	0	0	0	71	3	0	0
Asthma, bronchial	1	0.12	1	100.0	0	0	0	0	0	0	43	1
Caries, dental	58	7.01	50	86.2	0	0	8	13.7	55	45	61	13
Cirrhosis, hepatic	3	0.36	1	33.3	0	0	2	66.6	38	1	68	2
Dermatitis	7	0.84	6	85.7	0	0	1	14.2	55	5	41	2
Embolism, pulmonary	1	0.12	1	100.0	0	0	0	0	22	1	0	0
Emphysema, pulmonary	5	0.60	4	40.0	0	0	1	20.0	59	4	73	1
Epilepsy	3	0.36	3	100.0	0	0	0	0	42	3	0	0
Fractures	12	1.45	10	83.3	1	8.3	1	8.3	61	6	57	6
Hernia	8	0.96	7	87.5	0	0	1	12.5	58	7	56	1
Hypertension, essential	28	3.38	21	75.0	0	0	7	25.0	47	8	57	20
Hyperthyroidism	8	0.96	5	62.5	1	12.5	2	25.0	36	2	40	6
Morphinism	1	0.12	1	100.0	0	0	0	0	31	1	0	0
Neuritis	5	0.60	4	80.0	0	0	1	20.0	56	4	55	1
Neurasthenia	1	0.12	1	100.0	0	0	0	0	46	1	0	0
Optic complications	19	2.29	15	78.9	0	0	4	21.0	52	10	59	9
Osteoarthritis	4	0.48	4	100.0	0	0	0	0	64	3	77	1
Osteomyelitis	1	0.12	1	100.0	0	0	0	0	0	0	62	1
Pleurisy	2	0.24	1	50.0	0	0	1	50.0	18	1	58	1
Pregnancy	3	0.36	3	100.0	0	0	0	0	0	0	26	3
Psychosis	18	2.17	12	66.6	1	5.5	5	27.7	55	7	63	11
Scurvy	1	0.12	1	100.0	0	0	0	0	53	1	0	0
Singultus	1	0.12	1	100.0	0	0	0	0	45	1	0	0
Suicide	1	0.12	0	0	0	0	1	100.0	48	1	0	0
Surgical cases	4	0.48	4	100.0	0	0	0	0	25	2	39	2
Ulcer, peptic	1	0.12	0	0	0	0	1	100.0	41	1	0	0
Varices, hemorrhoids	8	0.96	8	100.0	0	0	0	0	49	4	54	4

Analysis of the Cases. Of the 827 cases of diabetes studied there were 146 (17.63 per cent) with no complication. As shown in Table 1, of the 146 uncomplicated cases 142 (97.26 per cent) improved and 3 (2.05 per cent) of them were unimproved. In 681 cases (82.37 per cent) there were one or more associated diseases. Of the 681 complicated cases 428 (69.2 per cent) died. The total number of complicating diseases was 75 and they are tabulated under 52 separate headings in Table 2. Table 2 indicates the various complications and shows the status of the patient after treatment. For the purpose of clearness the 75 types of complications are grouped under seven main heads, as follows: (*a*) Diabetic coma; (*b*) cardiorenal vascular diseases; (*c*) infections; (*d*) tuberculosis; (*e*) carcinoma; (*f*) syphilis; (*g*) miscellaneous.

The age and sex incidence of the group without complications is shown in Table 3, and that of the group with complications is furnished in Table 2. The number of males and females throughout the series was fairly equal except in the miscellaneous group which comprises 124 males and 86 females. In the entire series 453 were males and 374 females. The general average age of patients was computed for each type of complication. It is shown that the general average age ranged from 11 to 71 years, and that by far the most of the patients were over 45 years. Although the age incidence for this series of cases is high, nevertheless it conforms with the average age of the general population of the institution.

TABLE 3.—AGE AND SEX INCIDENCE OF DIABETIC PATIENTS WITHOUT COMPLICATIONS.

	No. of cases.	Average age of males.	No. of males.	Average age of females.	No. of females.	General average ages.	Youngest.	Oldest.
Total cases	146	40.8	72	47.1	74	43.9	7	78
Improved	142	40.8	71	46.7	71	43.8	7	78
Unimproved	3	0	0	55.3	3	55.3	50	63
Died	1	35.0	1	0	0	35.0	35	35

Diabetic Coma. Coma formerly was the outstanding complication of diabetes, but with modern treatment it can be controlled. Always there will be some deaths from coma, either because treatment is begun too late or because other complications develop which render the treatment for coma ineffective. In this analysis we have separated primary coma from secondary coma. It is obvious that the results of treatment will be much better in the primary than in the secondary group. As shown in Table 2, there were in all 33 cases of diabetic coma; of these 20 were of the primary and 13 were of the secondary variety. In the primary group 2 died and 18 recovered, while in the secondary group 10 died and 3 recov-

ered. A striking feature noted is that for primary coma the average age of males was 47, while the average age for females was 24 years. No female died in primary coma, and the ages of the 2 men dying in coma were 49 and 58 years respectively. None of our younger patients died in primary coma and all of them responded satisfactorily to treatment. In secondary coma the presence of overwhelming infections or of some other serious complications raised the mortality rate. The mortality figures of coma for the period of 1922 to 1926 were decidedly higher than those for the period of 1926 to 1930. A better understanding of the action of infection and fever upon insulin, an appreciation of the value of larger quantities of insulin and fluid in the treatment of coma and, finally, added clinical experience are among the chief reasons for a lower death rate during the past four years.

Cardiorenal Vascular Diseases. An inspection of Table 2 reveals that the cardiorenal vascular group with 273 cases constitutes the most common complication in this series. Gangrene occurred in 72 patients (8.7 per cent). Of these 35 (48.6 per cent) died. The total number of cases of gangrene occurring in the hospital population for the same period of time was 175. Of these 75 (42.8 per cent) died, showing a mortality rate that almost paralleled that of the diabetic group. The diseases of the heart and kidneys were for the most part produced by arteriosclerosis. There were 40 diabetics (4.8 per cent) with heart disease. Heart failure with death occurred in 22 (55 per cent) of them. During the period of time covered in this report there were 2871 cases of cardiac disease (5.7 per cent of the population of the hospital); 1069 (36.5 per cent) of them died. On comparing the percentage of patients suffering from cardiorenal vascular disorders in a public general hospital with that of diabetics who are affected in the same manner it would appear that there is little direct relationship between the two groups. However, the group of patients with diabetes and cardiac diseases showed a higher mortality rate by 18 per cent than the nondiabetic group. Undoubtedly, there is now a higher incidence of diabetes among patients with vascular diseases than was found before 1922. This fact may be explained on the assumption that the present-day diabetic more frequently lives on into the arteriosclerotic period of life by virtue of insulin than did the diabetic prior to the discovery of insulin.

Infections. A variety of infections other than gangrene were found in 86 cases, giving the group an incidence of 10.3 per cent. Any infection is borne badly by the diabetic, but pneumonia is an especially disastrous complication. There were 1200 patients with pneumonia admitted to the hospital during the period of this study and 654 (54.5 per cent) of them died. At the same time there were 16 diabetics with pneumonia and 14 (87.5 per cent) died. In 3 cases it was difficult to determine whether or not pneumonia was

present because acidosis was so severe. The changes in breathing and in the leukocyte counts were of the type easily confounded with those of advanced primary coma. Autopsy, however, was done in 2 of the 3 cases and the diagnosis of pneumonia was substantiated. Rheumatic fever is known to be a rare complication of diabetes. In this series no case of rheumatic fever was found. The occurrence of peptic ulcer in only 1 patient among our diabetics came as a distinct surprise, since there was an incidence of 167 cases of peptic ulcer in the hospital during the same period. One other patient had gastric hemorrhage and melena in the course of coma and a diagnosis of ulcer was made. At autopsy no ulcer was found.

Tuberculosis. Among our diabetics there were 40 cases of pulmonary tuberculosis or an incidence of 4.83 per cent. Sixteen of them died, giving a mortality rate of 40 per cent. Of the 40 diabetics who had tuberculosis 14 were considered to be free from tuberculosis when diabetes was first discovered, while 26 had both diabetes and tuberculosis when diabetes was diagnosed. Coincidently there were 1630 cases (3.26 per cent) of pulmonary tuberculosis among the hospital population, and of these 398 (24.4 per cent) died. Although the incidence of pulmonary tuberculosis is not much higher among the diabetic than among nondiabetic, yet the death rate is considerably greater in the diabetic group.

Carcinoma. Malignant disease occurred 8 times in our series, and it is noted that 4 of the patients died in the hospital. Carcinoma of the body and tail of the pancreas was found in 1 case. In other cases it appeared that diabetes had no relationship to the malignancy. Considering the frequency with which cancer appeared in the records of the hospital, we expected to find a higher rate of incidence of cancer among our diabetics. Eight hundred and sixty-two cases (1.7 per cent) admitted to the hospital during the period of this study had carcinoma. The mortality rate during their stay in the hospital for the total cases of carcinoma was 53.1 per cent and for the diabetic group it was 50 per cent.

Syphliis. Syphilis and diabetes were found together in 31 patients (3.74 per cent). Eight of the patients died, giving a mortality rate of 29 per cent for the group. The total number of syphilitics admitted to the hospital for this period was 1647 (3.3 per cent of all admissions). Of the total number of syphilitics admitted to the hospital 296 (18.1 per cent) died. Antisyphilitic treatment was followed by apparent recovery from diabetes in 2 syphilitic diabetics. In the other diabetics with syphilis antisyphilitic treatment appeared to have no effect on the diabetes other than that expected from any syphilitic under specific treatment.

Miscellaneous. Miscellaneous complications totalled 210 (25.39 per cent). Individually this group is not very impressive; but when considered collectively they constitute a serious problem in the successful management of the diabetics. The occurrence of hyper-

thyroidism only in 8 cases (0.96 per cent) was unexpected. It was thought that this complication would be more frequent in this district. There were 618 cases of hyperthyroidism (1.24 per cent of the entire hospital population treated in the hospital during this period of observation). For example, a study of 38 cases of diabetes combined with states of hyperthyroidism was reported by Wilder.[1] He found the association of diabetes and hyperthyroidism occurred with a frequency of about 1.1 per cent of all cases of hyperthyroidism. These figures, however, are not at variance with those cited by others who have reported upon the incidence of goiter and diabetes in the Middle West.

Discussion. It is obvious that a diagnosis of diabetes alone is often incomplete. When the diabetic's progress is unsatisfactory after he has been rendered sugar-free, a complication should be seriously considered. Many complications are easily detected, such as gangrene, apoplexy or carbuncles; but there are others, for example, early tuberculosis, carcinoma and coronary disease of the heart which often are hidden and which at times require careful examination to diagnose them. Uncomplicated diabetes usually is a benign disease that responds readily to routine treatment; but when a complication, especially one of an infectious nature, attacks the diabetic a comparatively benign disease becomes converted into a grave one. The prevention of complications should be the aim in the management of diabetics. Coma is largely preventable. Gangrene and infections often may be prevented.

The disparity between our mortality rate in coma and that of others who have reported on the subject may be explained partly by the advanced years of many of our patients. Our patients were, on the average, older than those seen in private practice. Furthermore, coma was usually far advanced before the patient was brought into the hospital. This is well illustrated in our 2 patients who died of primary coma; both had been in coma for more than 36 hours before entering the hospital.

When a discussion of one's mortality rate in coma arises a brief statement seems warranted regarding the method of management. In all of the cases of coma reported here insulin was used. The application of heat, the use of stimulants, eliminants and other adjuncts to treatment will not be discussed. During the earlier years of treatment with insulin the doses of insulin used were too small. Fear of insulin shock chiefly prevented the use of larger doses. Glucose solution and other fluids were not used in sufficient quantities to produce beneficial results. The successful treatment of coma depends upon the use of an adequate amount of insulin and a sufficient quantity of fluids to overcome acidosis and dehydration. For the past 4 years insulin in doses of 40 to 50 units had been given every 2 hours until the urine became sugar-free and the blood sugar was reduced to almost a normal level. Fluids are sup-

plied in large quantities. If the patient is in a precoma state diluted orange juice, tea, coffee or water are given by mouth in small quantities every half hour. It is unwise to give more than 100 cc. of fluid by mouth every half hour, because acute dilatation of the stomach may follow the administration of a large amount of fluid. When little or no fluids can be taken by mouth solutions of glucose and saline are given intravenously and subcutaneously, and plain water is given by rectum. One thousand cubic centimeters of 10 per cent glucose are administered intravenously, 1000 cc. of 1 per cent saline subcutaneously and 1000 cc. of water per rectum are given during the first 12 hours of treatment. It is our custom to add 1 unit of insulin for every 2 gm. of glucose directly to the intravenous solution. The solution is well agitated before it is given. This quantity of fluid usually is adequate to overcome the profound oliguria or anuria which are found in severe cases. An exception to this plan is made when a patient arrives in advanced coma. For this condition as high as 75 units are given intravenously at once, followed by 40 units every hour until the blood sugar begins to fall and the sugar in the urine becomes diminished. The periods then between doses of insulin are increased and the quantity decreased until the blood sugar is normal. Although no patient was seen who suffered any permanent ill effects from an overdose of insulin, nevertheless the reckless use of large quantities of insulin is to be condemned.

Alkalies were not given in any form to patients with acidosis. During the past 5 years we have given considerable attention to the kidney and the urinary excretion in diabetic coma. When anuria or profound oliguria develops in the presence of coma the prognosis is bad. The use of large quantities of fluid intravenously and by other routes frequently is followed by diuresis. The deciding factor in the success or failure of treatment often depends on this diuresis. Undoubtedly the relief of dehydration by administration of large quantities of fluids has not had sufficient attention in general. Lawrence[2] reported upon the beneficial effects of extremely large quantities of fluids in treating 2 desperate cases of coma. He used in 1 case 5300 cc. of fluids, and of that amount 4000 cc. were given intravenously during a period of 10 hours. Coburn[3] has recently emphasized the importance of diuresis in diabetic coma and states that in 18 per cent of his patients coma followed a renal shutdown. Warren,[4] pointed out that in coma the chief burden of eliminating acetone bodies is thrown on the kidneys, and that these substances profoundly injure the epithelium of the renal tubules.

Renal arteriosclerosis in a diabetic past 40 years is commonly found, and is frequently associated with a high renal threshold for sugar. Providing that renal insufficiency has not developed, large quantities of acetone and diacetic acid may be excreted with the urine. From clinical experience with coma one is led to believe

that when the injurious effect of acidosis is added to a kidney already damaged by arteriosclerosis the outcome of the disease often is fatal.

The disorders of the cardiorenal vascular type are among the commonest complications of diabetes. The reason for the high incidence of these complications is that both diabetes and the degenerative diseases of the cardiorenal-vascular system show a sharp rise between the ages of 40 to 55 years. The relationship between arteriosclerosis and myocardial disease is better understood now than ever before, but a breakdown of the cardiovascular system of the diabetic is often almost complete before it receives adequate attention. Since diabetes of older people is usually mild in type, complications such as the cardiovascular variety should especially be guarded against. Circulatory disturbances of the feet produced by arteriosclerosis are among the severest complications a diabetic may develop. Prevention of gangrene of the legs is one of the important functions of the attending physician. For prevention of gangrene Joslin[5] has stressed the importance of keeping the feet clean and avoiding even minor injuries to the feet. Despite careful treatment arteriosclerotic gangrene may develop.

The diabetic is more sensitive to the action of infection than is a normal person. Infections not only tend to develop more rapidly in the diabetic but they aggravate the diabetes itself. Whether infection makes diabetes worse by its action on metabolism in general, or by directly attacking the islands of Langerhans, has not been definitely decided. Infections favor the onset of acidosis and coma. However, infections are less feared today than formerly for the reason that with insulin acidosis and coma may be controlled. Larger doses of insulin are required to control hyperglycemia in the presence of fever and infections than are necessary in the afebrile patient. Pulmonary tuberculosis is found among diabetics less often today than formerly. Nevertheless, it is an important complication in our series. Sevringhaus,[6] of Madison, Wis., states that tuberculosis was found rarely in his series of 500 cases. The difference between his figures and ours is interesting because his patients come from the rural communities of Wisconsin while ours come exclusively from the industrial district of Milwaukee. Fitz[7] recently reported that he found 35 cases of tuberculosis among 1529 diabetics (2.3 per cent). He quotes Wilder and Adams, of The Mayo Clinic, who saw 10 cases of tuberculosis among 1000 diabetics (an incidence of 1 per cent). Of greatest importance is the fact that tuberculosis must always be thought of and sought for among diabetic patients. Its early diagnosis is necessary if a successful result is to be obtained. Of 150 diabetic deaths reported by Lyon[8] 11 (7.3 per cent) were caused by tuberculosis. Among Joslin's[5] first 3000 diabetics there were 84 true diabetic patients with tuberculosis and among the remaining 3000 there were 43 cases.

In his series the number of fatal cases of diabetes with tuberculosis was 103 (81.1 per cent of the total cases, 127). As to prognosis, it is generally conceded that the tuberculous diabetic does badly. Curschmann[9] is of the opinion that the tuberculous diabetic has about as good a chance for recovery as the nondiabetic. This opinion is not in accord with our own experience.

Most of the published reports classify syphilis as a rare complication of diabetes, yet our study showed a high incidence of syphilis. Joslin[10] states that there was a history of syphilis or signs of syphilis in 55 (1.7 per cent) of his 3200 diabetics, while Lemann[11] showed that 3.6 per cent of his cases had syphilis. He (Lemann) believes there is evidence to show that diabetes is in some cases produced by syphilitic disease of the pancreas. The incidence of latent syphilis and diabetes has been investigated by Warthin and Wilson.[12] Diabetes, they believed, was frequently produced by syphilis. They had postmortem evidences of syphilis in every one of 6 autopsies done in diabetics. Labbé[13] claims that the syphilitic diabetic is rare. The coincidence of syphilis with diabetes he found was no more frequent than syphilis with other diseases. The opinion among most writers appears to be that syphilis is a rare contributory cause of diabetes. Striking improvement in several syphilitic diabetics has been seen in our clinic after antisyphilitic treatment.

The high mortality figures cited in this series of cases require brief comment. A comparison of the death rate in this series was made with the death rate in an equal number of diabetic patients treated in private practice by one of us. It was estimated that the mortality rate in the series treated privately was 21.5 per cent, in contrast to a 35.7 per cent mortality reported here. Patients entering a county hospital belong to a class of people who, as a rule, neglect themselves. Many of them have no home and no money, and consequently they have irregular meals and sleep. Usually they enter the hospital in an advanced state of impoverishment. They frequently regard a painless disease like diabetes with indifference and, therefore, allow themselves to become undernourished. Complications become well established before the patient consults a doctor. Frequently these patients refuse hospital treatment until they are in the last stages of the disease. The result then is that diabetes itself, as well as the complication, is well advanced when the patient enters the hospital. Delay in beginning treatment has been one of the outstanding causes of death among these patients. One other factor which tended to raise our mortality rate was the advanced age of many patients. Older patients do not tolerate complications well. Coma in a young patient is comparatively easy to manage, but when coma develops in an old arteriosclerotic person with an infection it is more difficult to obtain satisfactory results from treatment.

Summary. 1. An analysis has been given of the complications present in 827 cases of diabetes mellitus. The 75 various types of complications are listed and discussed under seven main headings.

2. Of the 827 cases 681 (82.37 per cent) were complicated by one or more diseases. This shows that a diagnosis of diabetes mellitus alone is often incomplete.

3. A complication usually interferes with the welfare of a diabetic and often causes a disastrous outcome. For this reason the early recognition and treatment, as well as prevention, of complications are among the chief aims in the management of diabetes.

BIBLIOGRAPHY.

1. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med., 1926, **38**, 736.
2. Lawrence, R. D.: The Treatment of Desperate Cases of Diabetic Coma, Brit. Med. J., 1930, **1**, 690.
3. Coburn, A. F.: Diabetic Ketosis and Functional Renal Insufficiency, Am. J. Med. Sci., 1930, **180**, 178.
4. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930.
5. Joslin, E. P.: Treatment of Diabetes Mellitus, 4th ed., Philadelphia, Lea & Febiger, 1928, p. 742.
6. Sevringhaus, E.: Personal communication.
7. Fitz, R.: The Problem of Pulmonary Tuberculosis in Patients with Diabetes, Am. J. Med. Sci., 1930, **180**, 192.
8. Lyon, D. M.: Causes of Death Amongst Diabetics, Lancet, 1930, **2**, 293.
9. Curschmann, H.: Pulmonary Tuberculosis Complicating Diabetes, Beitr. z. klin. d. Tuberk., 1928, **69**, 540.
10. Joslin, E. P.: Treatment of Diabetes Mellitus, 4th ed., Philadelphia, Lea & Febiger, 1928, p. 753.
11. Lemann, I. I.: Relations of Syphilis and Diabetes to One Another, Am. J. Syph., 1929, **13**, 70.
12. Warthin, A. S., and Wilson, U. F.: Syphilis and Diabetes, Am. J. Med. Sci., 1916, **152**, 157.
13. Labbé, M.: Diabetes and Syphilis, Bull. Acad. de méd., 1923, **89**, 53.

A STUDY OF FIVE HUNDRED DIABETICS.*

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In the eight years since insulin has been available for our use 500 diabetic patients have been admitted to the Wisconsin General Hospital. These patients have been treated according to an essentially uniform plan. With a few exceptions, all have been under the care of the author during their hospital residence. With the assistance of Dr. W. S. Middleton a fundamental plan of therapy was developed during the first months of the insulin era. This has remained essentially unchanged throughout the series. This uni-

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formity of background should make some of the following data more significant.

Plan of Treatment. The diet plan of the hospital[1] involves the use of the Woodyatt type of ratios. The total fat is not allowed to vary significantly from the sum of twice the carbohydrate plus half the protein fed. Protein minimum is kept at 50 gm., except for infants. The calorie value of the diet is set at the minimum level which by trial will maintain approximately "normal" body weight. In obese cases alterations are made simply by reducing the fat content of such a prescribed diet to levels of 30 to 50 gm. daily. When the desired body weight has been reached the full fat quota is allowed again.

Admittedly there are many individuals who can economically use a higher fat ration, or proportionately less carbohydrate. It is dangerous to plan a routine type of therapy to include such unduly high fat diets. This is due not to the danger of ketosis or of fat intolerance but to the frequent objection of the patient to such a diet for continued use. The objection stated is general and will have specific exceptions. When our patients object to the carbohydrate limitation which we teach it is our practice to point out that the Woodyatt type of diet is economical in terms of insulin required, endogenous or injected. We frequently tell patients that they may have diets planned with larger amounts of carbohydrate and proportionately less fat. They understand that they will probably need more insulin on such diets. It is a very exceptional patient who elects to have more carbohydrate in the diet under these conditions.

It is impossible for us to tell how thoroughly and how persistently our patients follow their diets at home. Most of them return promptly to family physicians who have originally referred them to the hospital. Those who return for further care or who reply to letters of inquiry seem either to follow the diets faithfully or to be unwilling to submit to any restrictive routine at all.

We do not attempt to stop glycosuria by using undernutrition régimes followed by slow additions of food up to the requirement defined above. It appears economical of time to arrive as soon as possible at a maintenance diet, and to give insulin if necessary to stop loss of sugar. In many cases in which insulin is given at first it may be dispensed with before the discharge of the patient. There are other advantages to using insulin even though it may be dispensed with. In this way patients may learn under adequate supervision how to make the injections properly.

It is the aim to send patients home free from glycosuria. In young patients this is held to be inadequate as a goal, and the additional attempt is made to have the blood sugar before breakfast as near the normal level as is safe. The maximum insulin dosage allowed is insufficient to cause frequent reactions. Obviously there

are a few cases of very severe diabetes in young patients in whom not all these goals can be secured. In such a dilemma maintenance of weight, freedom from ketosis and avoidance of insulin reactions are the goals.

In no case is there any attempt to limit occupation or work. All patients are encouraged to get regular exercise and to make the amount of exercise as nearly uniform as possible each day.

Type of Cases Studied. With this general program we find that 59.8 per cent of our patients have required insulin at the time of discharge from the hospital. We are aware that a small number have been able to discontinue using insulin within the few weeks following hospitalization. Also eventually some of those who did not need insulin at first find it required after months at home, so that these factors more or less counteract each other. Of far greater influence on the above finding is the type of diabetics who are referred to this hospital. Those who can be controlled by simple dietary restrictions without weighed diets are almost never sent to the hospital, since the clientele is very largely drawn from outside the city of Madison. Consequently the above per cent figure for insulin requirement is far higher than for the diabetics of any normal community. There were 252 males and 248 females in this series.

The age incidence of cases is shown in Table 1. The age at onset is often unknown. The figure used is age at the time of admission to this hospital, which is commonly within a few months of the discovery of the disease. There is perhaps nothing unexpected[2] in the age distribution of cases.

Table 1.—Age Incidence of Diabetes and of Complications.

Decade.	Cases.		Pains, per cent.	Reduced reflexes, per cent.	Visual errors, per cent.	Gangrene, cases.
	Number.	Per cent.				
1	18	3.6	....	33	6	
2	62	12.4	5	45	32	
3	40	8.0	23	60	43	
4	51	10.2	35	47	45	2
5	74	14.8	46	46	46	4
6	110	22.0	46	39	41	12
7	107	21.4	41	45	37	21
8	38	7.6	53	61	32	11
Total	500	100.0	35.8	46	38.4	50
Last 75 cases	...	...	49	57.3	57.3	

Causes of Death. The further data as to deaths suggest several features for attention. The 90 deaths do not give a fair picture of mortality of diabetes in our 500 cases, since we have been unable to secure recent replies to a large number of requests for information from patients. These 90 cases are of interest primarily for a study of the causes of death. In 76 cases the causes are reasonably well

known. One-half of these, 38, died in this hospital. It is immediately evident that diabetes is not the only cause of death, for one-third of the 90 did not require insulin when in the hospital. Similarly, 13 (34 per cent) of the 38 who died in the hospital did not require insulin even at the time of death.

In classifying the causes of death there is some duplication, since sepsis and coma are inextricably mixed in a few of the younger patients. The "neglect after training" group also includes cases appearing again under other heads, such as "coma." By this neglect is meant that the patient, or, too often, the parents, showed gross neglect in following the instructions given. This must be accepted as a challenge to more thorough training, and to a more elaborate effort to keep the patient in touch with some physician who can assist him in maintaining his morale. Perhaps the most important factor is the persuading of the home physician that he can properly supervise the case after hospital training. General practitioners still need to have available simple instructions for the management of diabetic patients.

Those patients in this group who died in coma suffered from either neglect or severe infections occurring outside the hospital. Coma can no longer be looked on as the great cause of death in diabetes who have been hospital-trained. Infection plays a far more serious rôle. In the septic group pneumonia and infected gangrene each explain one-third of the mortality. Pneumonia occurs throughout the age groups, relatively more frequently in youth. Gangrene deaths appear naturally in the later decades only. It is surprising that tuberculosis appears so infrequently as a recognized cause of death. Besides these 4 tuberculous cases, there are known only 4 others with this infection in the total of 500 cases, 1 convalescing, 1 moribund, 1 recently discovered and 1 not heard from.

Gas gangrene has occurred in only 3 cases during hospital care. In each case the condition arose in the operative stump after amputation of a leg for septic gangrene. In 1 case the patient was a farmer and skin contamination with anaërobic bacteria could be reasonably suspected as the source of the infection. In the other cases the circumstances seem explainable only as the development of blood-borne organisms in devitalized tissue. In none of these cases was further surgical treatment permitted after gas was recognized, and the cases were consequently fatal.

It is of interest to note the causes of death in the diabetics who have died in coma in this hospital. There have been only 5 of these in the entire period since insulin was made available. One was moribund at the time of admission, with sepsis in the leg and cardiac decompensation. Two others were critically ill with pneumonia, which probably induced the coma. Another, a child, was readmitted in coma occurring during measles, and died within an hour with extensive bronchopneumonia. One boy was admitted in

coma, with an indefinite history of head injury in addition to known diabetes. His acidosis and ketosis were completely relieved, but consciousness was not restored. Postmortem examination, regrettably not including the head, revealed no cause for death. All coma cases have been treated without the use of alkali. Alkali has not appeared necessary in any of our cases. In an earlier paper[3] evidence has been presented to show that insulin, carbohydrate and fluid may be depended on to make available alkali from the circulating acetoacetate in the diabetic with ketosis. We see danger in the general use of alkali, but use saline freely in the cases with acidosis and dehydration.

Circulatory System. It is not surprising that so many deaths are attributable to the cardiovascular renal disease triad. The deaths from this group occurred in the age range where the incidence of diabetes increases, presumably from the arteriosclerotic process itself. The numerical magnitude of this group of deaths confirms the clinical impression that the efficiency of the circulatory system is a consideration of prime importance in the management of diabetics. Further evidence is secured from the frequency of gangrene in diabetics. (Table 1.) Ten per cent of all of our cases had gangrene at some time. Healing occurred in most of these. Since the treatment of arteriosclerosis and of myocardial diseases is not on the specific basis which obtains for diabetes, the circulatory system is often neglected. This neglect, due to pessimism, is not justified by the experience of those who carefully adjust the program of exercise and medication to individual needs. Again there are many physicians who feel that diabetes of arteriosclerotic origin is benign. This is usually true in the sense that it does not often lead to marked acidosis and death in coma. Such patients are most apt to die from vascular accidents, including gangrene, cardiac failure or pneumonia. But such reasoning should not lead to careless handling of the diabetes. The most important single factor in the integrity of the circulation is the power of the heart muscle. Muscle weakness in general, myocardial weakness included, is a feature of marked diabetes. Adequate diabetic therapy restores muscle power and endurance. The very presence of cardiac difficulty is, therefore, added reason for meticulous effort to obtain the best results in diabetic management. Individual results in restored capacity for work frequently corroborate this point of view. We have seen no reason to modify our plan of dietetic treatment for older patients because of the presence of arteriosclerosis. There is no evidence that high fat diets tend to produce sclerosis.

Neurologic Complications. Examination of the case histories of these 500 patients was made to determine the frequency of such disturbances as pains in the extremities, reduced patellar reflexes and transitory visual disturbances. (Table 1.) In many of the records no specific mention is made of one or more of these matters, hence the incidence of the phenomena in question is probably some-

what higher than the data indicate. During the latter part of the eight-year period involved more specific questions and examinations were used, since these complications had been found to be of surprising frequency. There is no sharp time limit for this change, hence all the records are included.

It has been impossible thus far to make any differentiation from the histories between pains due to "neuritis" and those associated with vascular disease. The impression gained is that a neuritis is far less common that paresthesia, hyperesthesia, cramp pain and aches of vague type. It is rare to find the sensory disturbance limited to any one or several distinct nerve supplies. Consequently all pains in extremities, without obvious causes such as arthritis, infection or trauma, are included in the group which numbers 35.8 per cent of all cases. This figure would be somewhat larger if early histories were more adequate in disclosing minor pains, or those to which patients had become accustomed. Such pains were present in 49 per cent of the last 75 cases studied. It has been necessary to use analgesic drugs for the relief of such pains in only a few cases. We have tried the alternate warm and cold applications to the legs with some success, and with only a few inconsequential bullous lesions from the heat employed. But the use of the Buerger passive exercises for the legs[4] has in most cases been of real symptomatic help. The relief from pains frequently does not become evident until the exercises have been used for three or four weeks. The age incidence of these pains, as shown in Table 2, indicates the probability that they are related in part, at least, to the vascular deficiency incident to sclerosis. Leg pains in the second and third decades are commonly of the cramp type and are promptly relieved when diabetic therapy is adequate.

TABLE 2.—CAUSES OF DEATH OF 76 DIABETICS.

Decade.	Deaths.	Neglect.	Coma.	Cardio-vascular renal disease.	Carcin-oma.	Septic processes.			
						Total.	Pneu-monia.	Tuber-culosis.	Post-gangren-ous.
1 . .	6	2	4	...	...	3	3		
2 . .	7	4	4	...	...	3	3		
3 . .	7	1	1	...	...	5	2	2	
4 . .	7	2	1	2	...	3	1	1	
5 . .	8	1	...	1	...	6	1	1	1
6 . .	23	...	1	4	1	9	2	...	3
7 . .	21	...	...	10	1	13	3	...	7
8 . .	11	...	...	3	1	4	1	...	4
Total .	90	10	11	20	3	46	16	4	15

The reduced or absent patellar reflexes have seldom been mentioned as a characteristic of diabetes. From the incidence of 46 per cent here shown it may be stated with confidence that careful

examination will reveal this disturbance of nervous function in a majority of diabetics, excluding only the very mild cases. The histories from which the above data are taken were in many cases inadequate to differentiate between normal and reduced intensity of reflex response. During the last four years the records show lively reflexes as 2+, reduced reflexes as 1+ and entire absence of the response with reënforcement as 0. Their entire absence is seen in a small group of cases, without evidence of luetic infection. In the last 75 diabetics examined reflexes were reduced or absent in 57.3 per cent. Inspection of the individual records in the matter of pains and reduced reflexes shows that there is no marked correlation between these two matters. Either occurs frequently without the other. In a few cases in young patients we have observed acute loss of reflexes to be followed by a return within a few weeks after treatment became established. From the results of Woltman and Wilder[5] we might expect the frequency of reflex disturbance to show an age incidence similar to that for pains. It is evident that the reduction of reflexes is far commoner in the first four decades than is pain. We assume that this means a disturbed plane of nutrition of the nervous tissue due to the diabetic process, in addition to which a sclerotic factor becomes common in older patients.

Visual Errors. The data on optic symptoms include all cases which reported amblyopia, scotomata, diplopia or decreased visual acuity which became marked at approximately the time other evidence of diabetes appeared. As far as possible cataract cases are not in this group, except where there was evidence of improvement in visual acuity without surgical attention to the eyes. In this matter again some cases are necessarily included in which the symptoms are not due to diabetes, and many are omitted because of the failure to ask specific questions in the original history-taking by students or interns. Whereas there were only 38.4 per cent of such visual defects in the whole series of 500, the last 75 cases reported difficulty in 57.3 per cent.

A surprising factor is the large number of cases with visual symptoms in patients of the first four decades. The records are inadequate to reveal the frequency with which good function was regained. It is now our expectation, based on the experience of the more recent years in this series of cases, that visual function will show a marked return toward the previous level of acuity. It is not uncommon to have patients find that they cannot read newspapers during the first week in the hospital, but that within two weeks vision is as good as usual. Refraction had been done in some cases, with satisfactory result until the diabetes was discovered and brought under control. Then vision rapidly altered to such an extent that lenses were a handicap, and no clinical refractive error existed. The more intimate details of this refractive change are now being studied. It is possible to say that the change is not only simply one of blood-sugar concentration or of ketosis, although

both these may be factors. There is a gradual progressive return of visual acuity which often takes more than two weeks to be complete. It is our practice to avoid fitting lenses until the patient has been free from glycosuria for a four-week period. We hope to make a further report on the significance of these eye changes under treatment.

Family History. In 20.4 per cent of these 500 cases a history of one or more diabetic members of the family was obtained. This figure obviously underrates the occurrence of other familial cases, since often only a casual question was asked, and inquiry at a later date might have secured information not available at the time of the first questioning. In 4 of the total series there was conjugal diabetes, that is, two couples were mildly diabetic (they were also obese).

Ketosis Before Treatment. Regardless of whether ketosis in the diabetic is held to mean inadequate fat oxidation or incomplete conversion of fat to carbohydrate, the occurrence of acetone bodies indicates severe diabetes. This can be evaluated in a prognostic way. We use the nitroprussid test without reinforcement by ammonium sulphate. Of our 500 cases there were 60.4 per cent who showed positive acetone tests at the time of admission. Following the dietary scheme outlined above, it was found necessary to use insulin at the time of discharge from the hospital in 84.4 per cent of this group of ketotic patients. Of the remainder of the cases which showed no ketosis on admission, it was found that insulin must be given according to the same criteria in only 22.2 per cent. Stated in other terms, when a patient is first examined and found to be diabetic, ketosis means that the chances are more than 5 to 1 that he will have to use insulin. If ketosis is not present the odds are almost 4 to 1 that insulin will not be needed. This early prognostic sign is of use in planning treatment, for if insulin is to be used it may as well be begun early to avoid delay. If it need not be used that knowledge is encouraging to the patient. The absence of ketosis may also be taken as evidence of relatively mild diabetes, and may, therefore, justify the postponement of a hospitalization for intensive treatment pending a trial of less marked dietary restrictions. Conversely the occurrence of ketosis should be taken as reason to insist on immediate and thorough efforts to meet the situation.

It is of some interest to examine the records of those nonketotic cases who nevertheless used insulin. There were 44 such cases. Six of these were given insulin for the definite purpose of shortening the hospital stay. In an unknown number of others the same factor was operative in part. Not infrequently improvement took place to such an extent that insulin was dispensed with. (This is occasionally true also of those cases with initial ketosis.) There were 3 thyrotoxic patients and 5 with infections of some magnitude included in the group of cases without ketosis who were given

insulin. Two-thirds of the remaining cases were over fifty years of age, and the insulin dosage was usually under 25 units per day. Only 5 cases of this group of 44 were given more than 25 units of insulin per day. It is evident, therefore, that the absence of ketosis is almost complete assurance against the need for insulin, unless there is such a complication as thyrotoxicosis or sepsis.

Summary. The study of the records of 500 diabetic patients seen in one institution in the eight years since insulin was made available shows that 60 per cent used insulin at discharge. Incidence of the disease and of 90 deaths is given by age decades. The causes of death include sepsis, cardiovascular renal disease and coma, in order of importance, as given. Gas gangrene occurred only three times. Pyogenic infection after gangrene and pneumonia are the commonest septic processes leading to death. Tuberculosis is infrequent. The significance of cardiovascular renal disease in the diabetic is discussed.

Pains in the extremities were found in 36 per cent and reduced or absent patellar reflexes in 46 per cent of the cases. Transitory visual disturbances were noted in 38 per cent.

The occurrence of ketosis at the time of admission or first examination is shown to be a good evidence of the need of insulin. Absence of ketosis is an equally reliable indication that insulin will not be needed.

REFERENCES.

1. Bach, M. T., and Sevringhaus, E. L.: Simplifying the Construction of Diets for Diabetic Patients, Modern Hospital, 1929, **33**, 132.
2. Joslin, E. P.: The Treatment of Diabetes Mellitus, Ed. 4, Philadelphia, Lea & Febiger, 1928, p. 138.
3. Sevringhaus, E. L., and Raube, H. A.: The Relief of Diabetic Acidosis by Insulin, J. Metab. Res., 1924, **5**, 263.
4. Joslin (footnote 2), p. 792.
5. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus. Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med., 1929, **44**, 576.

ANTIANEMIC INFLUENCE OF DESICCATED WHOLE HOG STOMACH.

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In 1926, Minot and Murphy[1] published their epochal observations of the favorable influence of a diet rich in liver tissue in the production of a continued remission in cases of pernicious anemia.

More recently, Sturgis and Isaacs[2] and Sharp[3] have announced that whole chopped hog stomach, desiccated and defatted with petroleum benzine, contains an antianemic factor quite comparable to that contained in liver.

The remarkable experiments of Castle and Locke[4] indicate that an antianemic enzyme-like substance is absent in the stomachs of persons with pernicious anemia. By feeding the incubated contents of a normal human stomach, recovered about 1 hour after the ingestion of raw beef muscle, to patients with pernicious anemia, Castle and Locke produced a reticulocyte response, an increase in erythrocytes and general clinical improvement, comparable to that which follows liver treatment. Patients with pernicious anemia to whom only finely divided raw beef muscle was fed experienced no improvement.

Conner[5] and Wilkinson[6] found that the ingestion of either raw or dried stomach gives essentially the same results. Renshaw,[7] Rosenow,[8] Snapper and Dupreez,[9] Meulengracht and Hecht-Johansen,[10] Hitzenberger,[11] Geuting,[12] Jagić and Klima,[13] Gödel,[14] Holbøll,[15] Decastello,[16] Leschke,[17] Faber[18] and Winge[19] have found that stomach therapy produces a prompt and lasting remission in cases of proved pernicious anemia. The therapeutic value of desiccated hog stomach tissue in pernicious anemia appears to be due to its ability to replace the absent enzyme-like blood-maturing substance in the stomach which normally acts as a constant stimulant to the blood-forming tissues.

In September, 1929, Dr. Cyrus C. Sturgis, of the University of Michigan, asked the writers to carry out an independent study of the therapeutic effect of desiccated hog stomach in cases of pernicious anemia, for the purpose of comparing results obtained at the Simpson Institute for Medical Research at Ann Arbor with those obtained in Dayton. During the past 18 months we have treated 15 patients with desiccated hog stomach,* with results which appear in Table 1, p. 321.

An inspection of this table will reveal the fact that desiccated hog stomach was effective in producing a satisfactory remission in every case. The most striking clinical and hematologic results were obtained in those cases in which the red blood cell count prior to treatment was below 2,000,000. The reticulocyte response was inversely proportionate to the initial red blood cell count; in the cases in which the first red blood cell count was very low (1,000,000 to 2,000,000) the reticulocyte response was greatest (23 to 41 per cent). In this respect the response to stomach therapy is similar to that observed following the ingestion of liver or liver extract.

Of particular importance is the observation that certain patients

* The material used (Ventriculin, N. N. R.) in the treatment of the first 10 patients was supplied, without cost, by Dr. E. A. Sharp, of Parke, Davis & Co., under whose direction it had been prepared.

with pernicious anemia who respond only to a moderate degree to liver therapy respond more favorably to stomach therapy. This was demonstrated in 2 of our cases (Nos. 14 and 15). Allerton,[20] Stokes,[21] Leschke,[17] Renshaw,[7] Snapper and Dupreez[9] and Isaacs, Sturgis and Rennie[22] have reported similar experiences in which the disease was but little influenced by liver or apparently potent liver extracts, but in which the substitution of dried stomach induced rapid subjective and hematologic improvement. Bertram[23] gave stomach powder to 11 patients with pernicious anemia; 10 responded favorably. In 1 case the stomach preparation was ineffective, whereas liver gave favorable results; Bertram assumes that this single failure might have been due to insufficient dosage. It is quite conceivable that occasional patients who do not respond to stomach therapy will respond to liver therapy.

TABLE 1.—RETICULOCYTE AND ERYTHROCYTE RESPONSE OF PATIENTS WITH PERNICIOUS ANEMIA TO DESICCATED WHOLE HOG STOMACH.

Patient No.	Before treatment.		Maximum per cent reticulocytes.	Days of treatment.	After treatment.	
	Red blood cells per c.mm.	Hemoglobin, per cent (Dare).			Red blood cells, per c.mm.	Hemoglobin, per cent (Dare).
1	940,000	20	36.4	62	3,810,000	78
2	1,240,000	30	31.0	58	4,320,000	82
3	1,260,000	29	27.0	69	4,040,000	84
4	1,330,000	33	29.7	60	4,840,000	88
5	1,460,000	30	24.6	85	5,100,000	86
6	1,540,000	41	16.6	124	4,080,000	76
7	1,690,000	48	41.0	48	4,050,000	82
8	1,750,000	40	23.0	56	4,800,000	86
9	1,760,000	40	17.6	53	4,340,000	80
10	1,850,000	30	11.0	44	3,740,000	68
11	1,960,000	40	15.8	72	4,810,000	79
12	2,080,000	48	15.9	63	3,240,000	74
13	2,430,000*	63	9.1	81	3,920,000	85
14	2,840,000†	58	3.9	84	4,510,000	86
15	2,940,000‡	57	3.4	98	3,870,000	80

* Discontinued stomach therapy for 1 month, during which time erythrocyte count dropped approximately 1,000,000.

† Count following 3 months of liver therapy.

‡ Count following 7 months of liver therapy.

Of the first 10 patients studied, 5 were given dilute hydrochloric acid in rather large amounts (1 dram in plain tea, to be sipped during each meal) in conjunction with the stomach therapy, while the other 5 patients were given no dilute hydrochloric acid. The addition of dilute hydrochloric acid was apparently without effect, and has not been employed since that time. All of the patients in this series showed a complete absence of free hydrochloric acid in the gastric content. Repeated gastric analyses during the course

of the dried stomach treatment showed no return of free hydrochloric acid.

Transfusion was done in 1 case just prior to the institution of stomach therapy, without appreciable benefit. The clinical improvement following the ingestion of desiccated stomach in this case was most striking. The advent of liver extract or desiccated stomach appears to have eliminated the need for transfusions in patients with pernicious anemia. In patients who are moribund, the introduction of desiccated stomach through a stomach tube appears to be more effective than transfusion.

With two outstanding exceptions, we found 30 gm. of desiccated stomach to be the optimum amount to be given each day to persons with initial red blood cell counts below 2,000,000. For practical purposes, Sturgis and Isaacs have adopted the dosage of 10 gm. of the dried powder for each million deficit in the red blood cell count (using 5,000,000 as the standard).

The 2 exceptional cases were patients of advanced age (68 and 74 years). In both instances the daily administration of 30 gm. of desiccated stomach for a period of 10 days was practically without influence upon the number of reticulocytes or red blood cells. By increasing the dosage to 40 gm. a day, a characteristic reticulocyte response and a progressive increase in the number of red blood cells resulted.

We encountered no difficulty in administering the dried stomach powder. Tomato juice appears to be the most acceptable vehicle, although any of the fruit juices may be used. The powder is insoluble in any of these substances, consequently it is necessary to make a uniform suspension of the powder in approximately a cupful of whatever liquid is employed. This is best done by stirring the powder into the liquid with a large spoon in a bowl. It seems advantageous to give the entire amount at one time each day. None of our patients has complained of any objectionable taste, nor has there been any aversion to continued use of the stomach preparation.

For practical purposes, we have adopted a single dose of 10 gm. daily as a maintenance dose after the red blood cell count has reached approximately 5,000,000. Certain patients are able to continue in a remission with 40 to 60 gm. per week. To determine the final maintenance dosage, individual study is necessary. It is important to impress upon the patient at the outset of the course of treatment the necessity of continuing the treatment for the balance of his lifetime.

Clinical Course During Treatment. The most striking feature of the treatment is the almost dramatic subjective improvement which occurs within the first 4 or 5 days following the initial administration of adequate amounts of the stomach powder. The anorexia, languor, mild fever, abnormal bowel movements and gastric distress rapidly

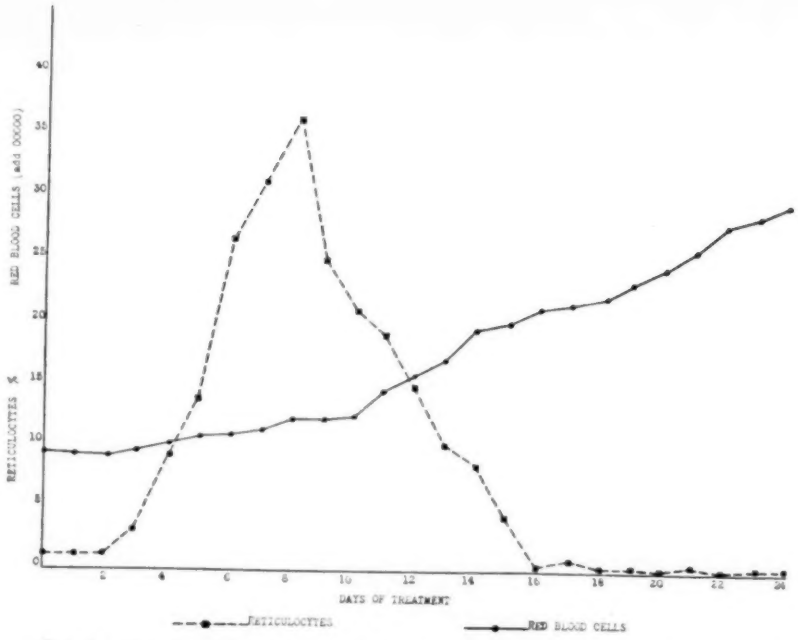

FIG. 1.—Case 1. Typical high reticulocyte response (36.4 per cent) to stomach therapy in a case of pernicious anemia in which the initial red blood cell count was relatively low (940,000).

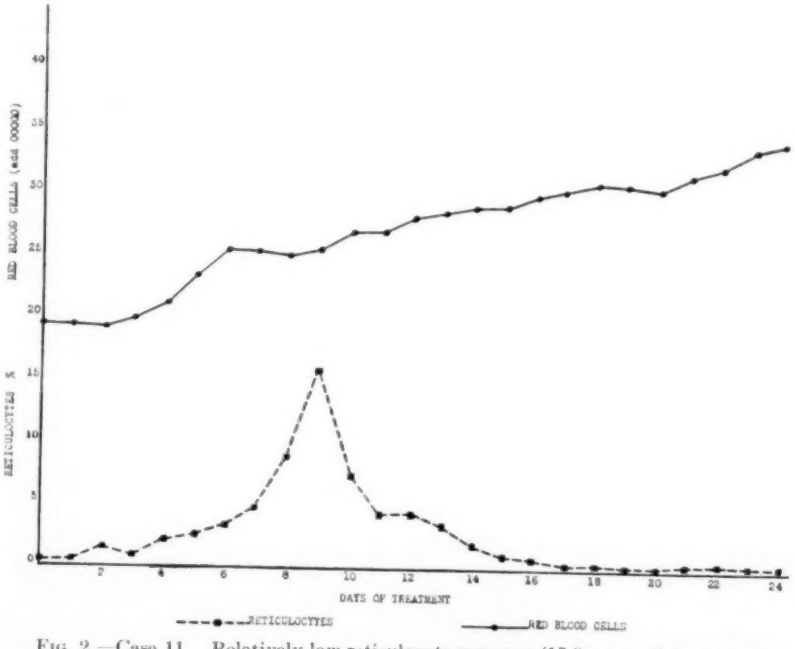

FIG. 2.—Case 11. Relatively low reticulocyte response (15.8 per cent) to stomach therapy in a case of pernicious anemia in which the initial red blood cell count was comparatively high (1,960,000).

disappear. The subicteric pigmentation of the skin and the marked pallor are gradually replaced by a more normal pink color, usually first observed in the skin over the pads of the distal segments of the fingers and toes, the skin of the palms and soles, the tip of the nose, chin and patches on each cheek. These skin changes usually occur before there is any significant increase in the red blood cell count or in the amount of hemoglobin, which probably indicates an early vasomotor influence.

If the neurologic manifestations of the disease are mild, consisting only of numbness and tingling of the hands and feet, these annoying symptoms will usually disappear, or be distinctly alleviated, within the course of a few days or weeks. Difficulties in locomotion due to loss of sensation in the joints are usually overcome to some degree. If the combined degenerative changes of the spinal cord are marked, to the extent of urinary and fecal incontinence, with the almost inevitable concomitant cystitis, little or no improvement of these more profound neurologic symptoms will occur. Five of our patients who had experienced numbness and tingling of the hands and feet for periods varying from 6 weeks to 5 months obtained complete relief from this annoying symptom; 3 others have experienced marked improvement. The neurologic manifestations of the disease have not progressed in any of our patients since the institution of desiccated stomach therapy. These observations lead us to conclude that it is imperative to maintain the erythrocyte count at the normal level in order to prevent further extension of preëxisting posterolateral sclerosis of the spinal cord.

The stimulating effect of the principle contained in desiccated stomach upon the hematopoietic system manifests itself about 3 to 5 days after treatment is begun by the production of a progressive increase in the percentage of immature red blood cells (reticulocytes). This wave of reticulocytosis usually reaches the crest from the seventh to the ninth day, after which the percentage of reticulocytes rapidly declines to the normal level. No significant rise in reticulocytes is to be anticipated if the erythrocyte count exceeds 3,000,000. The increase in mature erythrocytes usually begins during the reticulocyte rise and maintains a more or less steady increase of 400,000 to 500,000 per week. The determination of the percentage of reticulocytes each day during the first 10 or 12 days of treatment is of great value in that a satisfactory reticulocyte response indicates that effective blood regeneration is occurring.

If a patient who is thought to have pernicious anemia fails to develop a satisfactory reticulocytosis or other evidence of the anticipated remission following stomach or liver therapy, it is probable that one or more of the following factors is responsible for the failure: (1) Incorrect diagnosis; (2) inadequate dosage; (3) active infection; (4) impotent preparation; or (5) superimposed secondary anemia. The blood picture of pernicious anemia is occa-

sionally closely simulated by the anemia of syphilis, malaria, gastric or colonic carcinoma, hookworm or tapeworm infestations (particularly the broad tapeworm, *Dibothryocephalus latus*), hypothyroidism, aleukemic leukemia, splenic anemia, pregnancy and the puerperium, and the profound secondary anemia associated with prolonged chronic infection or dietary inadequacy. Sturgis and others have found that the presence of an acute or subacute infectious process may delay the reticulocyte response; as the infectious process subsides the red blood cell count usually progressively increases until the normal level is reached. Each new lot of the commercial preparation of desiccated stomach tissue (Ventriculin) is clinically tested and approved by the Simpson Memorial Institute, thus assuring a product of uniform potency. In the event of superimposed secondary anemia, iron therapy (ferrous carbonate, U. S. P., 2 gm. daily, or iron and ammonium citrate, U. S. P., 4 to 8 gm. daily) should be employed in addition to the stomach therapy.

Summary and Conclusions. 1. Desiccated defatted whole hog stomach in adequate dosage is effective in producing a prompt and continued remission in cases of pernicious anemia.

2. Occasional patients with pernicious anemia who do not respond completely to liver or its extract will obtain a more satisfactory response with stomach therapy.

3. The administration of dilute hydrochloric acid is apparently unnecessary in conjunction with stomach therapy. The advent of liver and stomach therapy appears to have eliminated the necessity for repeated transfusions in the treatment of pernicious anemia.

4. Certain patients of advanced age appear to require larger amounts of desiccated stomach for the production of an effective response than middle-aged patients.

5. We have encountered no patients who possessed an aversion to the continued use of desiccated stomach. The necessity for continuing adequate maintenance dosage throughout the remaining lifetime of the patient should be emphasized.

6. Mild neurologic symptoms disappeared or were distinctly alleviated in the 8 patients who experienced such symptoms prior to the institution of stomach therapy.

BIBLIOGRAPHY.

1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. Am. Med. Assn., 1926, **87**, 470.

2. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, J. Am. Med. Assn., 1929, **93**, 747.

3. Sharp, E. A.: An Antianemic Factor in Desiccated Stomach, J. Am. Med. Assn., 1929, **93**, 749.

4. Castle, W. B., and Locke, E. A.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia, J. Clin. Invest., 1928, **6**, 2-35. Castle, W. B.: Achlorhydria and Pernicious Anemia, Brit. Med. J., 1929, **1**, 1120; Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Administration to Patients With Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. Med. Sci., 1929, **178**, 748.

5. Conner, H. M.: The Treatment of Pernicious Anemia With Swine Stomach, J. Am. Med. Assn., 1930, **94**, 388; Further Observations on the Treatment of Pernicous Anemia With Gastric Tissue of Swine, Minnesota Med., 1930, **13**, 865; The Feeding of Gastric Tissue in the Treatment of Pernicious Anemia, J. Am. Med. Assn., 1931, **96**, 500.

6. Wilkinson, J. F.: Pernicious Anemia: Preliminary Reports on Results Obtained by Treatment With Certain Preparations of Stomach, Brit. Med. J., 1930, **1**, 236.

7. Renshaw, A.: Treatment of Pernicious Anemia With Desiccated Hog's Stomach, Brit. Med. J., 1930, **1**, 334.

8. Rosenow, G.: Behandlung der perniziösen Anämie mit getrocknetem Schweinemagen, Klin. Wchnschr., 1930, **9**, 652.

9. Snapper, I., and Dupreez, J. D. G.: Traitément de l'anémie pernicieuse par l'estomac de porc desséché et pulvérsé, Bull. et mém. Soc. méd. d. hôp. de Paris, 1930, **46**, 662.

10. Meulengracht, E., and Hecht-Johansen, A.: Behandlung der perniziösen Anämie mit Magen und Magenextrakt, Klin. Wchnschr., 1930, **9**, 1162.

11. Hitzenberger, Case Report, Proc. Gesellsch. f. inn. Med. in Wien, Wien. klin. Wchnschr., 1930, **43**, 283.

12. Geuting, H.: Die Behandlung der perniziösen Anämie mit einem Magensubstanz-Organpräparat (Stomopson), Deutsch. med. Wchnschr., 1930, **56**, 1219.

13. Jagic, N., and Klima, R.: Zur Therapie der perniziösen Anämie mit Ventraemon, Wien. klin. Wchnschr., 1930, **43**, 877.

14. Gödel, R.: Behandlung der perniziösen Anämie mit Ventraemon (Magenpräparat), Wien. klin. Wchnschr., 1930, **43**, 812.

15. Holbøll, S. A.: Treatment of Pernicious Anemia With Dried Stomach, Hospitalstidende, 1930, **73**, 825.

16. Decastello, A.: Erfahrungen über die Behandlung der perniziösen Anämie mit dem Magenpräparat Ventraemon, Med. Klin., 1930, **26**, 1444.

17. Leschke, E.: Die Magentherapie leberrefraktärer Fälle von perniziöser Anämie, Med. Klin., 1930, **26**, 1445.

18. Faber, K.: Pernicious Anemia: Treatment With Desiccated Stomach, Ugeskr. f. Læger, 1930, **92**, 467.

19. Winge, K.: Pernicious Anemia: Treatment With Desiccated Stomach, Ugeskr. f. Læger, 1930, **92**, 511.

20. Allerton, G. T.: Desiccated Hog's Stomach in Pernicious Anemia, Lancet, 1930, **219**, 759.

21. Stokes, C. E.: Desiccated Hog's Stomach in Pernicious Anemia, Brit. Med. J., 1930, **2**, 582.

22. Isaacs, R., Sturgis, C. C., and Rennie, T. A. C.: The Treatment of Pernicious Anemia (Addison-Biermer Type) With Desiccated Stomach, Folia Hæmatol., 1930, **42**, 397.

23. Bertram, F.: Klinisches zur Behandlung der Anämien mit Magenpräparaten, Klin. Wchnschr., 1930, **9**, 2103.

THE POSSIBLE CLINICAL INDICATIONS FOR FOLLICULAR HORMONE THERAPY BASED UPON ITS KNOWN BIOLOGIC EFFECT IN ANIMAL EXPERIMENTS.

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As a result of the international researches carried out in the last 10 years, it has now been firmly established that the female sexual cycle of warm-blooded animals is controlled by the interaction of

the hormones of the anterior pituitary and of the ovaries. In spite, however, of all the work which has been done, the exact nature of this mechanism in all its details is not yet clear. It is, however, definitely known that under the influence of the anterior pituitary the hormone is produced even in the ovaries of infantile individuals and, as a result, the female genital organs become mature and the secondary sex characteristics, both physical and psychologic, develop. Loewe was right in describing it as the hormone which confers the stamp of femininity, and since it is produced in large quantities at the time of maturation of the Graafian follicles, it is also called the "follicular hormone."

In view of the far-reaching effect of this hormone many investigators have thought it might be the only hormone produced by the female reproductive glands and therefore named it "the female sex hormone." However, it has now been shown that the ovaries must produce a second hormone in order to ensure the complete sexual function of the female organism. This is produced in the corpus luteum. Its function is to stimulate production of the decidua and thus prepare the uterus, which has proliferated under influence of the follicular hormone, for the nidation of the fertilized ova and to assure their further development.

I. **Chemistry of Follicular Hormone.** The follicular hormone was first obtained in the crystalline form by Doisy from the urine of pregnant women. Butenandt considers that chemically the hormone is a triple unsaturated oxyketone, probably of the stearin series, with the formula $C_{18}H_{22}O_2$ (Fig. 1).

It is interesting to note that Marrian has isolated from the urine of pregnant women a second form of this hormone, with the formula $C_{18}H_{24}O_3$ and considers this to be a double unsaturated trivalent alcohol (Fig. 2). His product "Œstrin," therefore, contains 1 molecule of water more, which is joined to 1 of the 3 double bonds of the first form. According to both Butenandt and Marrian, the efficacy of Œstrin is about one-fifth that of the hormone $C_{18}H_{22}O_2$. Whether Œstrin represents an excreted form of the hormone, for which there is considerable evidence, cannot be definitely stated at present; in any case Butenandt has succeeded in converting Œstrin into the more potent form by hydrolysis, a fact which establishes the structural relationship of the two forms of hormone. Commercial preparations produced from the urine of pregnant women may contain both forms side by side. Doisy has suggested the name Theelin for the crystalline hormone with the formula $C_{18}H_{22}O_2$.

II. **Action of the Follicular Hormone.** The effect of the follicular hormone is manifested in several ways: In castrated animals with extensive degeneration of the sexual organs and other physical and psychic changes, by the administration of the follicular hormone these changes may be prevented. Furthermore, in infantile female

animals a premature development of the sexual organs (Fallopian tubes, uterus, vagina, mamma) may be produced by means of the hormone.

In the following communication these effects will be described separately.

(*a*) *Effect on the Vagina.* The changes which the follicular hormone produces in the vaginæ of rodents is already well known since it constitutes the basis of the Allen-Doisy test. The introduction of the vaginal smear test by these two American workers has opened up a new and fruitful era in the progress of sexual hormone research.

The premature development of the infantile vagina into a sexually mature organ, which results from the administration of the follicular hormone *per os*, is shown in the accompanying illustrations (Fig. 3). Figure 3 shows a section through the vagina of an untreated infantile monkey (Macacus rhesus). The vaginal walls are in apposition and have but few folds; they are covered with a low pavement epithelium composed of four to eight layers and showing no cornification Fig. 4). Figure 4 represents a section through the vagina of an animal of the same age which had been treated for a month with a total amount of 2000 rat units of follicular hormone. The lumen of the much-hypertrophied vagina is filled with horny epithelial cells. The epithelium itself is composed of many layers, the upper ones being mostly horny. The whole mucous membrane shows many fossæ and folds. In the untreated animal the surface of the epithelium is parallel to the submucosa and only in a few places shows the formation of papillæ, whereas the submucosa of the treated animal is thrust out in the form of papillary bodies. In the control animal the submucosa consists of dense and poorly-vascularized connective tissue. In the treated animal, on the contrary, the cells of the submucosa are loosely packed and there are many blood-vessels. There are abundant smooth muscle fibers in its outer layer.

(*b*) *Effect on the Uterus.* By the administration of the follicular hormone the uterus of an infantile castrated female can be brought to the same condition which it normally shows in the sexually mature animal during the first rupture of the follicles. This point will be discussed in greater detail in a later section in connection with the corpus luteum hormone. It will suffice here to briefly describe the appearance of the uterus in the above-mentioned experiments on infantile monkeys (Figs. 5 and 6). In contradistinction to the control animal, the uterus of the monkey which received 2000 rat units of follicular hormone is much larger and markedly more hyperemic. Whereas in the submucosa of the untreated animal there are only a few straight glandular tubules to be seen, numerous racemose tubules with high cylindrical epithelium can be observed in the submucosa of the treated animal. The endometrium of the untreated animal shows a single layer of low cylindrical epithelium, while the endometrium of the treated animal shows high cylindrical

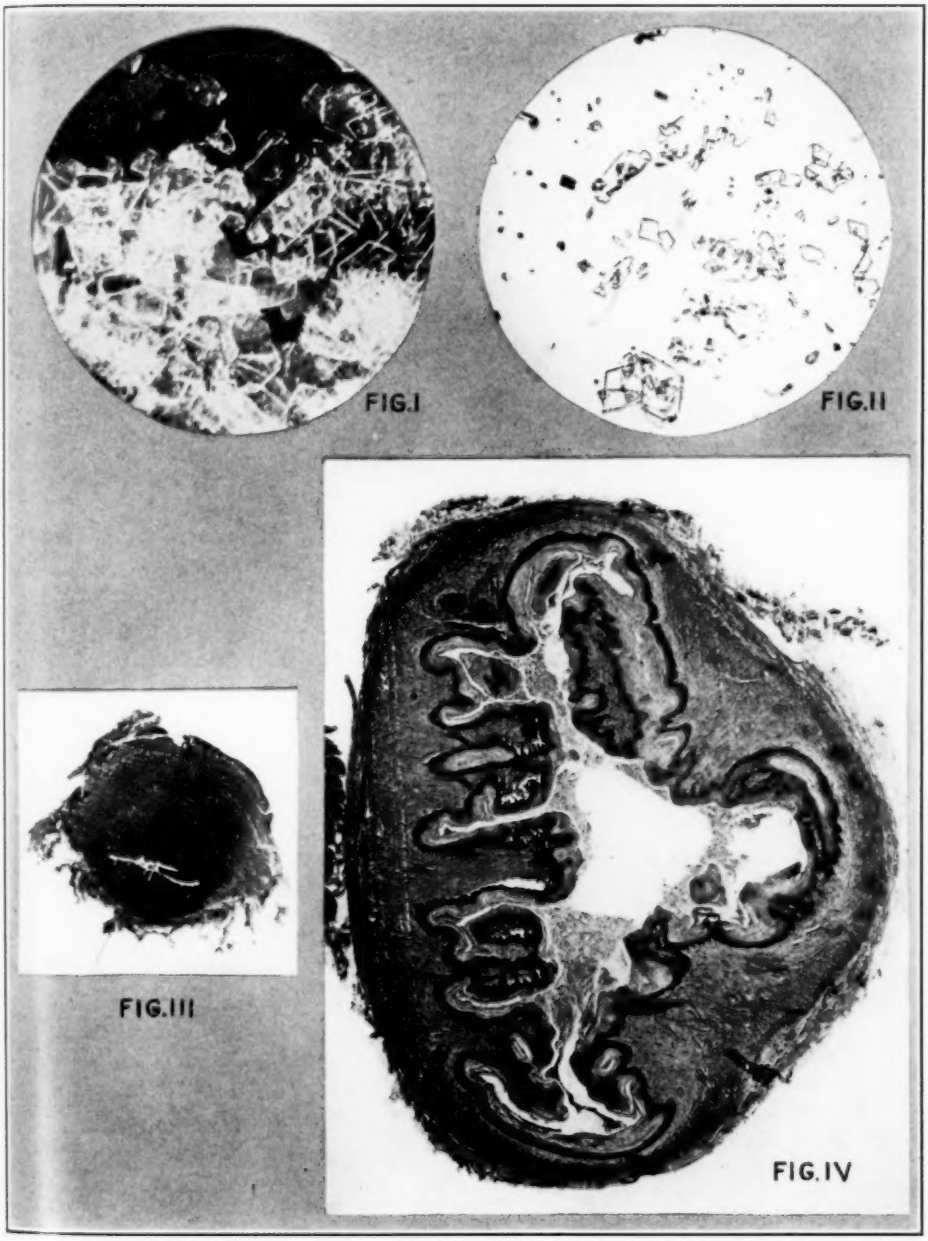

Fig. 1.—Crystalline follicular hormone $C_{18}H_{22}O_2$; 1 gm. = 8 million mouse units.
Fig. 2.—Crystalline follicular hormone $C_{18}H_{24}O_2$ (Œstrin); 1 gm. = 1.6 million mouse units.
Fig. 3.—Vagina of an infantile monkey.
Fig. 4.—Vagina of an infantile monkey after 4 weeks' peroral treatment with a total of 2000 rat units follicular hormone.

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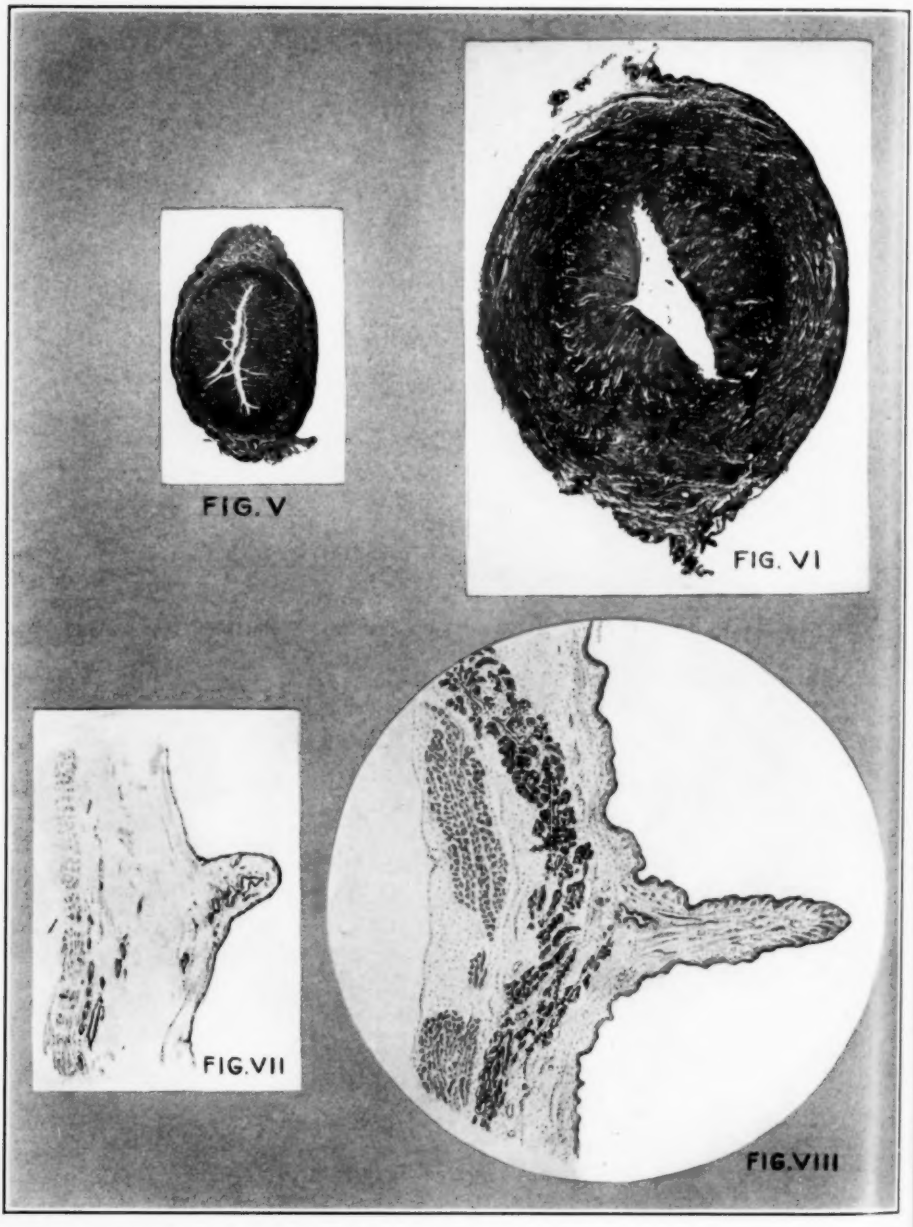


FIG. 5.—Uterus of an infantile monkey.

FIG. 6.—Uterus of an infantile monkey after 4 weeks' peroral treatment with a total of 2000 rat units follicular hormone.

FIG. 7.—Mamma of an infantile castrated guinea pig.

FIG. 8.—Mamma of an infantile castrated guinea pig after peroral treatment with follicular hormone.

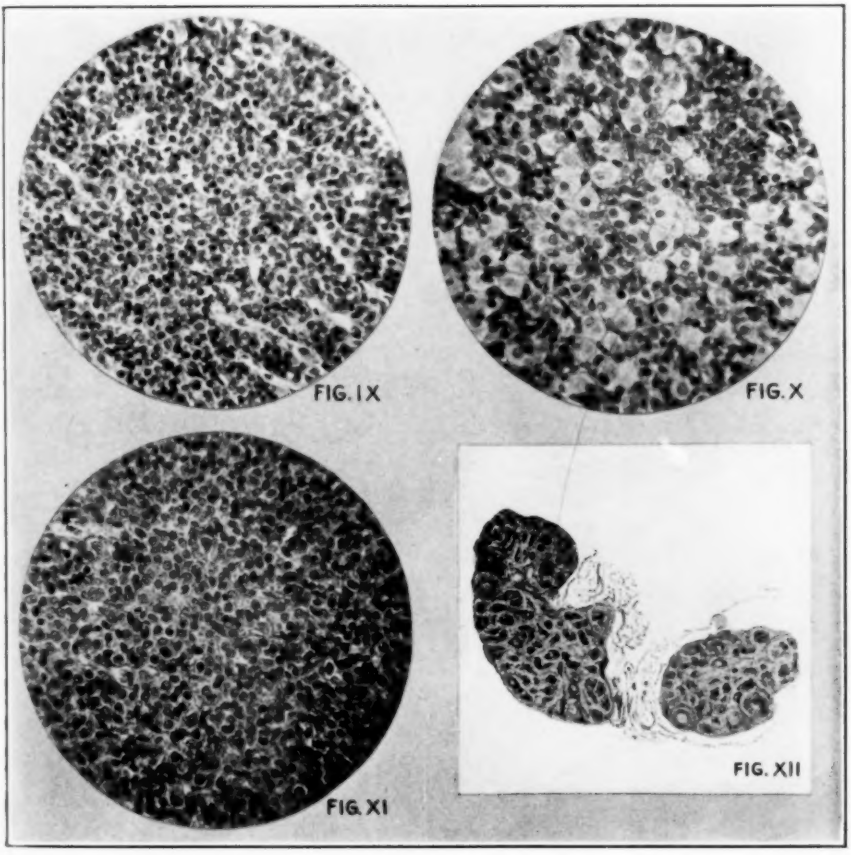


FIG. 9.—Anterior pituitary of an infantile female rat.

FIG. 10.—Anterior pituitary of an infantile female rat 3 weeks after castration.

FIG. 11.—Anterior pituitary of an infantile female rat which was treated with follicular hormone after castration.

FIG. 12.—Ovary of senile female rat removed before beginning follicular hormone treatment.

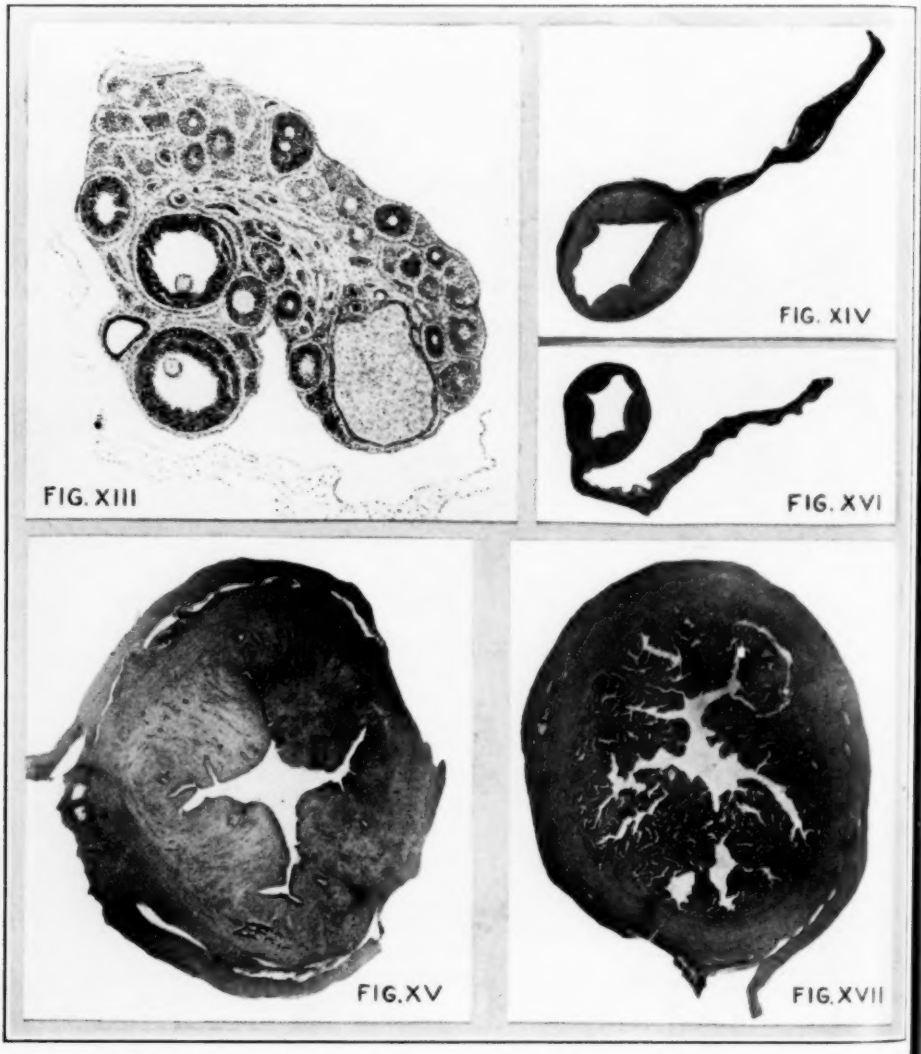


FIG. 13.—The second ovary of the same animal 3 months after beginning follicular hormone treatment.
FIG. 14.—Uterus of an infantile rabbit.
FIG. 15.—Uterus of an infantile rabbit after treatment with physiologic doses of follicular hormone.
FIG. 16.—Uterus of an infantile rabbit after treatment with 1 rabbit unit of corpus luteum hormone.
FIG. 17.—Uterus of an infantile female rabbit, treated first with physiologic doses of follicular hormone and then with 1 rabbit unit of corpus luteum hormone.

cells. The hyperemic effect of hormone treatment is shown by the considerable increase in number and size of the bloodvessels in the parametrium of the treated animal. Robertson, Maddux and Allen obtained, by parenteral administration of about one-fifth of the peroral dose to castrated female monkeys, in principle the same effects.

(*c*) *Effect on the Mammæ.* The follicular hormone can also produce in the mammæ of infantile castrates a condition corresponding to that found in the adult mature female during the resting stage.

Figures 7 and 8 show sections through the mammæ of an untreated infantile castrated guinea pig and of its sister which had received the follicular hormone *per os* subsequent to castration. In the untreated animal the mamma and nipple is small and undeveloped. In the loose subcutaneous connective tissue isolated undeveloped glands are found lined with low epithelium. The superficial epithelium is undeveloped. The nipples are ill-defined. In the treated animal the whole mammary gland is much enlarged. The subcutaneous fat contains fully-developed clusters of tubules, the acini of which are lined with high epithelium. The superficial epithelium is higher and shows fully-developed nipples.

(*d*) *Effect on the Anterior Pituitary.* The formation of the ovarian hormone depends on the presence of the anterior pituitary hormone. The functional activity of the anterior pituitary is also modified to a certain extent by the hormones produced by the ovary.

Following castration marked changes occur in the anterior pituitary both in infantile and adult females, which can be made to disappear by treatment with follicular hormone (Figs. 9, 10 and 11). Figures 9, 10 and 11 clearly demonstrate this fact. This change in the anterior pituitary after castration and the possibility of preventing or reversing it by means of the follicular hormone can be used to determine the amount of hormone produced by the infantile ovary. In castrated infantile female rats the daily administration of one-thirtieth of a rat unit suffices to prevent the appearance of "castration cells" in the anterior pituitary, whereas a daily dose of one-fifteenth of a rat unit is enough to produce slight signs of rut. The amount of hormone produced by the infantile ovary must therefore lie within the above limits. Since the castration changes in the hypophysis correspond to a considerable increase in the production of the anterior pituitary hormone, and since the administration of follicular hormone is capable of reversing both the histologic changes and the increased functional activity of the anterior pituitary, it follows that the follicular hormone produced by the ovary exerts directly or indirectly a regulating influence on the hormone production of the anterior pituitary, whereby a hormonal equilibrium is maintained between the two glands.

(*e*) *General Effect.* The generalized changes (habitus, mental attitude) which occur after castration show that the reproductive glands have an influence on the body as a whole in addition to their

effect on the sexual organs. Possibly this effect is connected with the action on the whole endocrine system. Experimental proof of this generalized endocrine effect of the follicular hormone is well demonstrated in the work of Steinach, Kun and Hohlweg (*Pflüger's Arch.*, vol. **219**, No. 2, p. 325).

The duration of individual "heat periods" in senile rats was controlled by daily vaginal smears and at the same time the body weight, percentage of hemoglobin and red cell count were ascertained. In these animals the heat cycle occurred at increasingly long intervals and finally ceased altogether. The body weight, hemoglobin percentage and red cell count slowly fell. Treatment with follicular hormone was commenced only when no "estral cycle" had been observed for several months. One ovary and part of a uterine horn were removed at the beginning of treatment. After an interval of a few days the senile animals were then injected with a sufficient dose of follicular hormone to produce a regular alternation of "heat" and resting periods such as is found in normal sexually mature animals. Four weeks after the commencement of treatment, growth of hair on previously bald patches, increase in weight and a higher red cell count and hemoglobin percentage were already definitely noticeable. After 2 to 4 months' treatment, when reactivation had made considerable progress (*e. g.*, increase in weight from 203 to 237 gm., increase of hemoglobin from 70 to 90 per cent and of red cells from 6.6 to 8.7 millions, within 3 months), the occurrence of autogenous "heat periods" was first observed after suspension of treatment. The prolonged administration of follicular hormone must evidently impart so strong a stimulus to the whole endocrine system that, as a result, the maturation of follicles and the formation of corpora lutea and the consequent production of follicular and corpus luteum hormones can take place in the ovary itself (Figs. 12 and 13). Figures 12 and 13 show the ovary of a senile rat before and after treatment with follicular hormone. The increased agility, higher metabolic rate and greater alertness of the treated animal are further indications of the general reactivation.

Changes in the distribution of the blood in the body can also be classed as a part of the general effects of the follicular hormone. K. Junkmann obtained the following results in a series of experiments on the action of the hormone on the gut. He found that it had no influence whatever on peristalsis in the isolated intestine. Also in rabbits treated with follicular hormone there is no difference in the behavior of the gut as regards peristalsis nor in its reactions to various excitant and inhibitory pharmacologic reagents, in comparison with the intestines of normal and castrated controls. On the other hand, there was a very marked hyperemia of the whole intestine of the animal treated with follicular hormone. It is conceivable that this improvement in the circulation would favorably influence spastic conditions which are due to a poor blood supply.

It will be seen, therefore, that apart from its direct effect on the sexual organs, the follicular hormone exercises a marked influence on the functional activity of the body as a whole, which influence is easily explainable by the close interdependence of the various units of the whole endocrine system.

(*f*) *Synergism with the Corpus Luteum.* According to our present knowledge the ovary produces the follicular hormone only until the time of sexual maturity, since it can be shown that complete development of the female genital system may be brought about by the artificial administration of the follicular hormone. Nevertheless, in order that it may be able to receive the fertilized ovum and to make possible the further development of the latter, the uterus must undergo a further change which consists in the formation of a decidua. This change is brought about by the hormone produced by the corpus luteum. Fraenkel has proved that the corpus luteum is an endocrine gland, the function of which is to bring about the implantation and further development of the fertilized ovum. Corner and Allen were the first observers to confirm this statement in experiments with corpus luteum extracts. Working in conjunction with us on a purified corpus luteum extract, C. Clauberg has closely investigated the combined action on the uterus of the follicular and corpus luteum hormones. As a result of our researches we found that unless the uterus has been brought to the normal condition of proliferation by means of physiologic doses of the follicular hormone, the corpus luteum cannot produce decidual changes in the uterine mucous membrane.

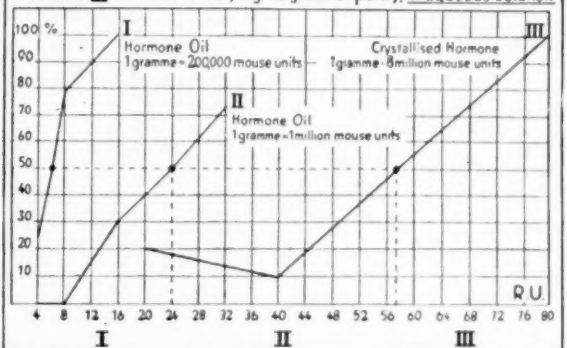
The normal proliferative dose for the uterus of the adult castrated rabbit was experimentally calculated by Clauberg to be 105 mouse* units, which were administered in doses of 10, 15, 15, 20, 20 and 25 mouse units, spread over 6 days. Smaller or larger doses produce an insufficient or a pathologic proliferation respectively and it is then impossible to produce the normal decidual changes with the subsequent administration of corpus luteum hormone (Figs. 14, 15, 16 and 17). Figures 14, 15, 16 and 17 show the effect on the uterus of an infantile rabbit of separate and of combined treatment with follicular and luteal hormone respectively.

According to our present knowledge, menstruation in man represents the disintegration of the decidual mucous membrane of the uterus; we hope, therefore, that by means of combined treatment with physiologic doses of follicular and corpus luteum hormone, we shall be able to produce in a castrated woman the development of decidual changes in the uterine mucosa, which must finally result in the occurrence of menstruation. Clinical investigations directed to ascertaining the necessary physiologic dosage of the two hormones are at present in progress.

* Five mouse units are equal to one rat unit.

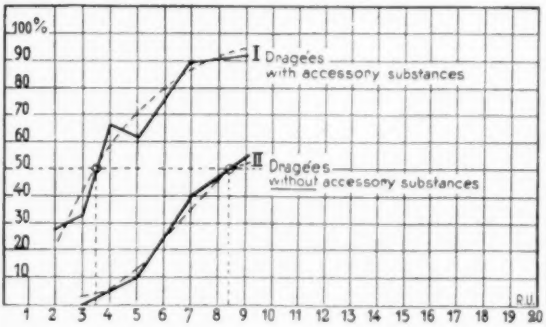
III. **Possible Methods of Administering the Follicular Hormone.** The stability of the follicular hormone makes it possible to administer it not only parenterally, but also *per os*, *per rectum*, *per vaginam* and *via* the skin. Since apart from parenteral administration the most important method for therapeutic purposes is the peroral route, we carried out an extensive series of animal experiments on this

Table 1 Hormone in varying degrees of purity, in aqueous solution



I				II				III			
No of units	No of animals	No showing oestrus	%	No of units	No of animals	No showing oestrus	%	No of units	No of animals	No showing oestrus	%
4	15	4	27	4	12	0	0	20	10	2	20
8	14	11	78	8	12	0	0	40	10	1	10
16	15	15	100	16	12	4	30	80	10	10	100
				32	11	8	73				

Table 2 Emulsions of 2 different dragée types



I				II			
No of units	No of Animals	No showing oestrus	%	No of units	No of Animals	No showing oestrus	%
2	30	8	27	3	20	0	0
3	30	9	33	5	20	2	10
4	29	20	67	7	20	8	40
5	30	19	65	9	20	11	55
7	29	26	89				
	30	28	95				

point. The favorable results of peroral administration of follicular hormone are partly demonstrated in the foregoing illustrations. Particularly worthy of note, however, are the results of our experiments on the relation between the presence of certain concomitant substances and the effect of peroral administration (Tables 1 and 2). In Table 1 a comparison is made between the peroral effect of hormone products having a hormone content of 2.5 per cent, 12.5 per cent and 100 per cent respectively (in comparison with the crystalline hormone). *The crystalline product was by far the least effective.* In Table 2 the effectiveness of follicular hormone dragées with and without the addition of certain substances favorable to absorption, is shown. In the case of the dragées which were free from concomitants, 8.5 units were required to produce estrus in 50 per cent of the experimental animals, whereas in the dragées which contained concomitants favorable to absorption, only 3.5 units were sufficient.

It will be seen from the figures given in the tables that the preliminary experiments were carried out on a very large number of animals. Our subsequent experiments fully confirmed the results obtained. The necessary peroral dose of Progynon dragées showed a practically constant relationship to the subcutaneous dose of 4 to 1. These animal experiments would appear to justify the peroral administration of the hormone in human therapy.

IV. **The Therapeutic Outlook.** Animal experiments have clearly shown that the complete development of female characteristics in an individual is only to be expected when the follicular hormone is produced in adequate amounts. Follicular hormone therapy is, therefore, justifiable in all cases due to ovarian hypofunction.

Climacteric changes form the chief indication for follicular hormone therapy, and it will also favorably influence conditions due to partial or complete artificial suppression of ovarian function.

In this connection the relief of vasomotor disturbances, which form a frequent and distressing symptom, is most important. The symptom complex is not, however, confined to the cardiovascular system. Cutaneous manifestations such as pruritus and eczema, intestinal symptoms in the form of severe constipation, arthritic conditions which are refractory to antirheumatic treatment, are all met with and form a most favorable field for substitution therapy with the follicular hormone. Mental changes, especially the frequently-occurring psychic depression, are also benefited. Here the generalized tonic effect of the follicular hormone undoubtedly plays an important part since, in addition to readjusting local disturbances, it produces a condition of euphoria which is in full harmony with the somatic regeneration which successful hormone treatment produces in women. This general rejuvenation has also been observed in elderly women in whom the climacteric symptoms have already subsided.

Menstrual disorders which appear in the form of secondary amenorrhea, oligomenorrhea, dysmenorrhea, etc., constitute a further

indication for this therapy. In agreement with the experimental evidence of the effect of the follicular hormone on the whole endocrine system, clinical experience shows that the hormone is often capable of reëstablishing a regular menstrual cycle. The many different forms which menstrual disorders may assume make it impossible for us to discuss the clinical aspect in detail.

Many cases in which follicular hormone therapy has proved a failure can often be explained on our knowledge of the mechanism of the physiologic action of the hormone which we have above described. For example, one cannot expect the follicular hormone alone to produce phenomena which are a function of its action combined with that of the corpus luteum hormone, which we have previously described.

Also, in cases of primary amenorrhea due to complete absence of development of the sexual organs, the administration of follicular hormone will be ineffective since it will find no adequate point of attack in the body.

It would also be fallacious to apply follicular hormone therapy in cases in which amenorrhea is the expression of a natural reaction to such conditions as advanced phthisis, cachexia, etc. Apart from these contraindications there is no danger attached to the employment of follicular hormone therapy.

REFERENCES.

1. Allen, E., and Doisy, E. A.: J. Am. Med. Assn., 1923, **81**, 819.
2. Butenandt: Abhandl. d. Gesell. d. Wissensch. z. Göttingen, Math.-physikal. Klasse, Ser. 3, No. 2.
3. Clauberg, C.: Zentralbl. f. Gynäk., 1930, **54**, 7, 1154, 2757; 1931, **55**, 1459.
4. Corner, G. W., and Allen, W. M.: Am. J. Physiol., 1929, **88**, 326.
5. Fraenkel, L.: Arch. f. Gynäk., 1903, **86**, 439; 1910, **91**, 705.
6. Hohlweg, W., and Dohrn, M.: Wien. f. inn. Med., 1931, **21**, 323.
7. Marrian, G. F.: Biochem. J., 1929, **23**, 1090; 1930, **24**, 435, 1021.
8. Robertson, D. L., Maddux, W. P., and Allen, E.: Endocrinol., 1930, **14**, 77.
9. Schoeller, W., Dohrn, M., and Hohlweg, W.: Med. J. and Rec., 1930, **132**, 487.
10. Steinach, E., Kun, H., and Hohlweg, W.: Pflüger's Arch. f. ges. Phys., 1928, **219**, 325.

ABNORMALITIES IN THE WHITE BLOOD CELL RESPONSE. (LEUKEMOID, ATYPICAL LEUKEMIC AND LEUKOPENIC BLOOD PICTURES.)

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During the past 5 years there have been, on the wards of the Presbyterian Hospital, an unusually varied group of cases presenting abnormal white blood cell pictures. In many instances the type

of blood picture observed has not fulfilled the requirements for diagnosis. Because of the interest aroused in attempting to classify these changes and because of the difficulty in understanding the underlying situation, these cases have been collected. In this paper a selected number will be presented with the impressions that have developed.

The leukocytes usually respond promptly to the introduction of certain foreign agents into the body, whether these agents be relatively simple chemical compounds, or the complicated products of infection. Some of these foreign agents usually produce a leukocytosis, others a leukopenia. Many of these responses have been sufficiently observed and recorded that they have now been incorporated into our clinical conceptions as part of the expected and anticipated reaction in disease. Thus, a leukocytosis is expected in pneumonia, a leukopenia in typhoid fever, an eosinophilia in trichiniasis. These are considered as normal white blood cell responses to these infections.

Other less common leukocytic responses have also been observed and their clinical significance accepted. Young polymorphonuclear leukocytes, occasional myelocytes, and even rare myeloblasts are seen from time to time during the course of a severe infection. The presence of these immature forms is usually thought of as representing the output of an overacting, overstimulated bone marrow. The serious significance of leukopenia, occurring during the course of diseases usually associated with leukocytosis, is widely appreciated. We have recently come to view the syndrome known as glandular fever more as an unusual lymphocytic response to a transient throat infection than as a primary blood disease.

Stimulation of Leukopoiesis. The following cases are presented as examples of unusual responses on the part of the white blood cell elements of the hematopoietic system to stimulation. The cases are presented in order, beginning with mild transient abnormalities in the blood picture, proceeding to cases satisfying the present requirements for the diagnosis of leukemia.

Case Reports.—Case 1. T. K., Unit 72505. A young clerk, aged 19 years, was admitted on July 8, 1928, for the repair of a right indirect, inguinal hernia. A blood count at this time showed a normal number of cells and normal differential. The hernia was repaired and the cord transplanted. His postoperative course was quiet except for a slight, persistent, unexplained temperature, thought possibly to be associated with a mild cough. He was discharged on July 29, 21 days after operation, in good condition, with normal temperature, with a small sinus in the wound.

After 3 days at home his temperature rose and he felt feverish and sick. He was readmitted on August 7 with a temperature of 104° F., pulse 120, definitely enlarged spleen, and tenderness and induration of the cord and right testis. His white count was 5800 with 70 per cent lymphocytes, no abnormal cells being seen. Blood cultures were negative and although the diagnosis of typhoid fever was considered, it was felt that his high fever was best explained by an acute orchitis. Five days later the white

count was 6600 with 72 per cent lymphocytes. The red count was normal throughout. Operation revealed an acute, suppurative, gangrenous testicle which was removed, with drainage of the infected area. The day after operation his temperature was 103.6° F., white blood cells were 10,900, 72 per cent lymphocytes. No abnormal cells were seen. His temperature rapidly returned to normal, as did the white count and differential. Ten days after operation, the white count was 10,600; lymphocytes, 32 per cent; polymorphonuclears 60 per cent. Culture of the wound grew staphylococcus albus.

This patient who was readmitted 1 month after operation with a high fever and strange white blood count presented a puzzling diagnostic problem solved only by exploration of the operative wound. It is of interest that a man, who, only a few weeks before, had a normal white blood count, should have developed this response to gangrene of the testicle.

Case 2.—Dr. I. H., Unit 70074. A member of the house staff, aged 26 years, was admitted complaining of a mild gastrointestinal upset with a temperature of 101° F. On admission his only abnormal physical finding was a distinctly tender, easily palpable spleen. White blood cells, 9900; 75 per cent polymorphonuclears; 18 per cent lymphocytes; 3 per cent monocytes; 4 per cent myelocytes; and 1 per cent myeloblasts. The evening of admission he became chilly; his temperature rose to 102.4° F., and he complained of slight soreness of the throat and moderate drowsiness. His throat appeared normal but his gums were slightly red and boggy. There was no superficial glandular enlargement, but the spleen was still very tender. A white count taken at that time showed 7900 white cells, 74 per cent polymorphonuclears, 15 per cent myelocytes, 1 per cent myeloblasts. The following day he felt distinctly better. The temperature had fallen to 100° F. White cells were 9200, 79 per cent polymorphonuclears, 10 per cent myelocytes. Three days after admission his temperature was normal, he felt and looked well, tenderness of his spleen had largely disappeared, and his white cells had fallen to 4200 with 64 per cent polymorphonuclears and only 2.5 per cent myelocytes.

He was discharged on the day following and was without symptoms for 6 months when he developed a sore throat with generalized aches and pains, suggesting influenza. His white count at that time was 8500 with 10 per cent myelocytes. The tip of his spleen was palpable and slightly tender. The symptoms and abnormal physical signs rapidly disappeared. One week later the white blood cells numbered 10,000; polymorphonuclears, 63 per cent. No myelocytes were seen. He has now been well for over a year.

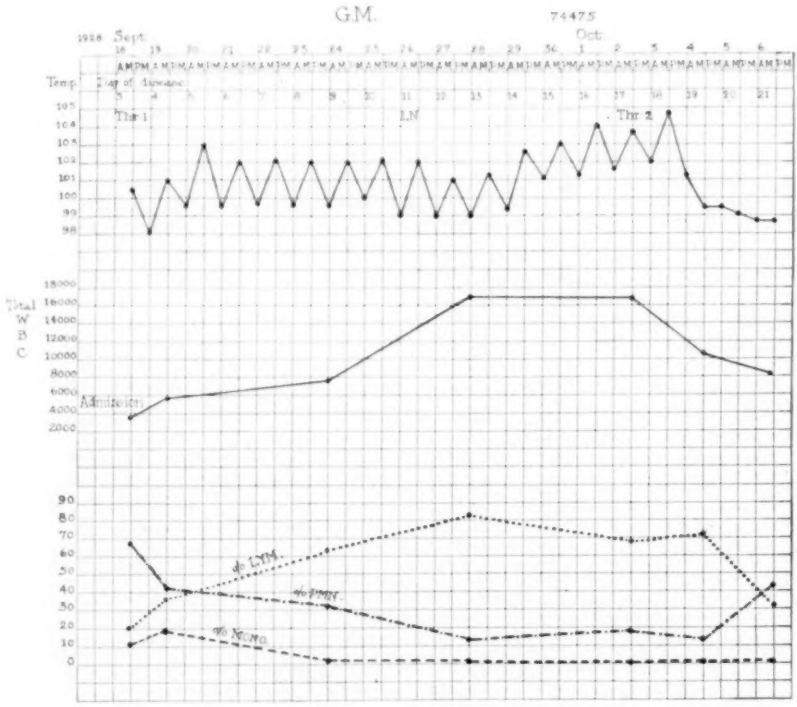
Case 3.—E. C., Unit 70610. A negro housewife, aged 48 years, was admitted with a 6-day history of fever, cough, and pain in the chest. On admission there was a temperature of 102.4° F. and physical signs of pharyngitis and bronchitis. There was also a small aneurysm of the innominate artery, thought to be associated with the 4+ Wassermann. On admission she had a red count of 4,000,000; a white count of 36,000 with 85 per cent polymorphonuclears and 12 per cent myelocytes and myeloblasts. Three days later her symptoms had subsided, her temperature was normal, and her physical signs had disappeared. Her white count had fallen to 10,500; polymorphonuclears, 87 per cent; immature cells, 2 per cent. She was discharged a week later without symptoms, with a white count of 6800; polymorphonuclears, 78 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent.

While under antiluetic treatment in the out-patient department, during

the 2 years since discharge, she has been examined at 6-month intervals and found normal.

CASE 4.—G. M., Unit 74475. An American salesman, aged 23 years, entered the hospital with a 3-day complaint of scattered aches and pains, mild chilly sensations, and fever. The admission diagnosis was grippe. Examination revealed a well-developed and well-nourished young man looking acutely ill. His throat was slightly injected and the cervical lymph nodes were moderately enlarged. The temperature curve and the white blood count are shown in the accompanying chart. (Chart I.) During the second week of his stay in the hospital, there was considerable further increase in

CHART I.



LN, appearance of enlarged lymph nodes. Thr., appearance of pharyngitis.

the size of the cervical lymph nodes, together with moderate enlargement of the axillary and inguinal nodes and spleen. At this time several whitish spots were observed on the posterior pharyngeal wall. These disappeared promptly after the return of temperature to normal. Two blood cultures taken during the febrile stage were negative.

He was seen in the medical follow-up 4 months after discharge from the wards, at which time he was without symptoms or abnormal physical signs.

This case probably represents a slight variation from the group of cases of glandular fever. The preliminary leukopenia, although

described in glandular fever, is not the usual white blood cell response in that condition.

Typical cases of glandular fever, conforming in all respects to the published descriptions, might be included at this point as further examples of queer leukocytic reactions to throat infection. Several examples of this syndrome have been seen, but, as this clinical picture is now so well established, it is felt that analysis of these cases would be unnecessary here.

The preceding cases represent relatively mild, transiently abnormal hematopoietic responses with prompt return of the blood picture to normal and recovery of the patient. The following cases show a more severe and progressively abnormal response of the hematopoietic system with ultimate death of the patient.

CASE 5.—M. H., Unit 54731. A school girl, aged 13 years, was admitted with an 11-day history of ulcerative stomatitis. Her past history was irrelevant except for the fact that she had been losing weight for a year. On admission she was acutely ill and showed ulcers of the buccal mucous membrane. Her red count was 2,000,000; hemoglobin, 45 per cent. Platelets numbered 11,000. White blood cells were 2400; 20 per cent polymorphonuclears, 17 per cent lymphocytes. Sixty-three per cent of the cells were immature forms thought to be myelocytes and myeloblasts. Oxidase stain showed that many of these abnormal cells contained granules. She became rapidly worse. Her gums became spongy and boggy. There were frequent nose bleeds. The lymph nodes and spleen, which at first were not enlarged, increased rapidly in size, became tender, and she died 10 days after admission with what was thought clinically to be an acute myeloblastic leukemia. Blood cultures were negative. Hemolytic and nonhemolytic streptococci were isolated from the ulcers in the mouth.

At autopsy an extensive, acute, caseating tuberculosis involving chiefly the lymph nodes and spleen was found, with terminal dissemination. The bone marrow was hyperplastic. There was no evidence of any kind of the changes found in acute leukemia. The final anatomic diagnosis was recorded as tuberculosis of the lymph nodes, spleen, liver, kidney, Fallopian tubes, and lung; gangrenous stomatitis and gingivitis; petechial hemorrhages of skin, pericardium and pleura; hyperplastic bone marrow. Morphologically typical tubercle bacilli were demonstrated in the microscopic sections.

CASE 6.—W. H., Unit 74853. A policeman, aged 57 years, was admitted complaining of progressive weakness, loss of 25 pounds in weight, an unproductive cough without fever, over a period of 1 month. He had also noticed progressive enlargement of his left upper abdomen. Physical examination showed a chronically ill man with obvious loss of weight, an enlarged liver extending 6 cm. below the costal margin, and a very large, hard spleen extending to the iliac crest. His red count was 3,400,000 with 65 per cent hemoglobin. White cells numbered 70,000, polymorphonuclears, 61 per cent; monocytes, 8 per cent; lymphocytes, 13 per cent; basophils, 8 per cent; with basophilic myelocytes, 3 per cent. There were 6 per cent eosinophils with 1 per cent eosinophilic myelocytes. There was moderate anisocytosis and poikilocytosis and marked polychromatophilia. He was admitted as a case of chronic myelogenous leukemia. Bleeding and clotting times were normal. There was no fever during the 3 weeks' stay in the hospital. He was then discharged to be followed in the out-patient department, receiving radiotherapy.

He was readmitted 5 months later complaining of weakness and a dry

cough of 2 weeks' duration. His temperature was 102° F. There was a slight dullness and diminished breath sounds over the left lower lobe posteriorly. Roentgen ray of the chest showed diffuse peribronchial infiltration radiating outward from both hila. His red count was 4,000,000. His white count had fallen gradually during the preceding months and was now 5500, 86 per cent polymorphonuclears, 8 per cent myelocytes, 6 per cent lymphocytes. There was an apparent increase in the number of platelets. It was felt that he had a lobular pneumonia and that the altered white count resulted from radiotherapy. His spleen was considerably smaller than on his previous admission, reaching but 7½ cm. below the costal margin. During the 3½-week stay in the hospital, he ran an irregular fever, reaching 104° nearly every day. Indefinite signs persisted in his chest. He lost ground rather rapidly and died. In spite of 2 transfusions, his white count just before death was 2160 with 76 per cent polymorphonuclears, 17 per cent myelocytes, 3 per cent myeloblasts. His final red count was 4,520,000. Platelets were still reported as increased. Blood cultures throughout his terminal illness were negative. His sputum grew out hemolytic streptococcus and was negative for tubercle bacilli on 2 separate examinations. At the time of death it was believed that he had a typical, chronic myelocytic leukemia with a terminal pulmonary infection, the nature of which was not determined, but which was thought, from the physical signs and Roentgen rays, to be a lobular pneumonia.

Autopsy revealed an extensive tuberculosis, involving chiefly the spleen and lymph glands, with an acute generalized miliary process and a tuberculous pneumonia. The process in the spleen appeared to be the oldest tuberculous lesion. Numerous tubercle bacilli were found in the microscopic sections. Nowhere could any lesion be found to indicate myeloid leukemia.

Case 7.—H. S., Unit 70905. A chauffeur, aged 58 years, was first admitted in February, 1928, with a month's history of fever and pain in the chest. He had a mild secondary anemia. The white count on several examinations was within normal limits. No abnormal cells were seen. There were physical signs of a right pleurisy with effusion. Aspiration of the chest resulted in the unexpected presence of thick, foul pus from which an anaërobic streptococcus was isolated. Thoracotomy was performed and the cavity drained. He was discharged 3 months after operation, in satisfactory condition, and he returned to work.

He was readmitted in July, 1929, with a month's history of weakness and fever. Examination revealed at this time a sallow, anemic man without other abnormal physical findings. The red count was 3,000,000; hemoglobin, 65 per cent. White blood cells, 1900; polymorphonuclears, 20 per cent; lymphocytes, 72 per cent, and monocytes, 8 per cent. No abnormal or young forms were seen. The symptoms persisted and were accompanied by a moderate swinging fever, rarely rising above 101° F. The white blood count remained about as on admission, as did the red count, both being transiently elevated after transfusion. Two weeks after admission several slightly enlarged lymph nodes were observed, one of which was removed, sectioned and diagnosed as chronic lymphadenitis. Roentgen rays of the chest showed a moderate increase in the hilum lymph nodes and this, together with the weakness and the anemia, suggested the possibility of Hodgkin's disease. He was discharged on September 15, still undiagnosed and unimproved.

He returned on October 8, distinctly worse, but still without definite physical signs, except for the presence of a small amount of fluid in the left chest. Red count was 2,700,000, 55 per cent hemoglobin. His white blood cells had altered surprisingly and now numbered 13,000, 9 per cent polymorphonuclears, 48 per cent lymphocytes, and 43 per cent myeloblasts.

He was thought to belong to the group of leukosarcomata because of the leukemic type of blood picture and the presence by Roentgen ray of a rapidly increasing mediastinal tumor. He failed rapidly and died on the 23d of October.

At autopsy he was found to have the typical microscopic lesions of acute myeloblastic leukemia. In addition, it was found that the enlarged hilum lymph nodes were the site of extensive caseous tuberculosis with a terminal tuberculous pneumonia and generalized miliary dissemination. It was felt that the case probably represented one of chronic progressive tuberculosis of the hilum lymph nodes, spleen and other lymph nodes, with terminal spread, in which an acute myeloid leukemia had developed.

CASE 8.—V. B., Unit 227639. A Canadian bank clerk, aged 23 years, came in on November 6, 1929, with a 9-day history of mild cold and a 3-day history of high fever and a sore mouth and throat. There had been no chill or chest pains and no cough. His past history was irrelevant. He presented the appearance of a prostrated, dyspneic, desperately ill young white man. His temperature was 105° F.; pulse, 112; respirations, 34. His gums, tongue, buccal and pharyngeal mucous membranes were the site of a severe necrotizing infection. There were signs of lobular pneumonia in both lungs. Examination was otherwise negative. There were no petechiæ. Repeated blood cultures and blood Wassermann were negative. He had a normal red blood count and hemoglobin throughout. His white count was 26,000 on admission and slowly fell to 11,000 4 days later when he died.

In all the smears there were many young polymorphonuclears and rare myelocytes. There were, in addition, between 15 and 25 per cent of large, definitely abnormal white cells. Some of these were thought to be embryonic monocytes, but most of them could not be classified.

Autopsy revealed a necrotizing infection involving the entire respiratory apparatus with early gangrene of both lungs. The bone marrow was hyperplastic and contained many young white blood cells, as did the spleen. It was felt by the pathologists that the case could not be definitely grouped as an acute leukemia, but that that condition was closely approximated. Cultures were unsatisfactory and Gram stains of the microscopic sections revealed many organisms, none of which could be identified as predominating.

Clinically this patient presented a rapidly spreading, necrotizing infection of the mouth, throat, and lungs. The presence of the large number of abnormal white cells, together with myelocytes and young polymorphonuclears suggested antemortem the possibility of a coincident acute leukemia. Postmortem, the hyperplastic bone marrow and the presence of many immature white blood cells in the spleen also suggested leukemia.

This case was classified by the attending physician and by the pathologic staff as a leukemoid type of reaction to a severe infection and not as an acute leukemia. Both groups, however, felt that the blood dyscrasia as well as some of the microscopic lesions strongly suggested the presence of true leukemia and that these pathologic changes very nearly satisfied the existing requirements for making that diagnosis.

CASE 9.—J. G., Unit 69160. An American stenographer, aged 20 years, who came in complaining of trouble with the teeth, bleeding and soreness of gums, increasing weakness and pallor of 6 months' duration. On admission she had a slight fever and was definitely pale. There were small superficial ulcers in the mouth; the gums were spongy and red. There were no

petechiæ but there was a small purpuric eruption over the leg. The tip of the spleen was just palpable. There was a slight enlargement of the cervical and axillary lymph nodes. On admission the red blood cells were 3,600,000, 75 per cent hemoglobin. White blood cells were 14,200, 85 per cent myeloblasts. Vigorous treatment of the lesions in her mouth and gums was immediately instituted. Three days after admission the white blood cells were 10,000, 60 per cent myeloblasts. The lesions in the mouth and gums showed improvement. A week after admission her white count had fallen to 6000 with 46 per cent myeloblasts. A week later further improvement was noted in the condition of her gums and mouth. At this time her white count was 3000, 75 per cent polymorphonuclears, 10 per cent lymphocytes, and only 1 per cent myeloblasts. Petechiæ which had appeared a week previously, disappeared temporarily at this time. Then quite suddenly the mouth lesions became very much worse. A severe ulceration of the gums set in. Her temperature rose rapidly and she died 4 weeks after admission. Her final blood count showed 20,000 white cells with 75 per cent myeloblasts and only 5 per cent polymorphonuclears. Blood cultures on 2 occasions were negative. Attempts to isolate the organisms from her gums were unsuccessful. No Vincent's organisms were found. The final clinical diagnosis was acute leukemia. Autopsy was refused.

The possible relationship between acute infectious mouth lesions and leukemia has often been suggested, and it is of interest here that the patient showed distinct, though transient, improvement in her general condition as well as a definite return of the blood picture toward normal during the time that her mouth lesions appeared to be responding to vigorous local therapy.

Case 10.—M. L., Unit 79151. An American cashier, aged 58 years, was admitted with a 4-day history of abdominal pain, obstipation and frequent vomiting. On admission he was *in extremis*. His spleen was palpable 4 cm. below the costal margin. Physical examination was otherwise negative. Red blood cells numbered 4,000,000 with 75 per cent hemoglobin. Platelets were normal. White blood cells were 2700 with 75 per cent polymorphonuclears, 15 per cent lymphocytes, and 10 per cent monocytes. Blood culture was negative. He died shortly after admission with a clinical diagnosis of acute intestinal obstruction. At autopsy a very unusual streptococcus infection of the duodenum was found, causing obstruction at this point. Microscopically the liver showed marked periportal accumulation of lymphocytes, a picture identical with that seen in lymphatic leukemia. No other evidence of leukemia, however, was seen.

A case of rapidly fatal streptococcus duodenitis showing a depression in the total number of white blood cells without the presence of abnormal forms in the blood. The point of interest is that one of the standard anatomic requirements for the diagnosis of lymphatic leukemia was present.

Case 11.—J. D., Unit 63220. A young American boy who was followed in the Presbyterian Hospital from the age of 2, when he was found to have chronic bronchitis, rickets, and hypertrophy of the tonsils. His tonsils were removed and for several years he was without symptoms, except for a mild persistent cough.

At the age of 8 he came in with a short history of abdominal pain and vomiting. There was considerable tenderness in the right lower quadrant and it was felt by the surgeons that he had a typical acute appendicitis.

The red blood cells at that time were normal but the white blood cells numbered 39,000, of which 42 per cent were polymorphonuclear, 14 per cent lymphocytes, 34 per cent monocytes, and 10 per cent myelocytes. This blood count was repeated with the same results. In view of the strange count, operation was withheld and the symptoms and signs of appendicitis slowly disappeared.

During the next 2 years he was never entirely well, did not gain weight as he should, and had persistent cough. He was closely followed during this period, his white blood cells ranging between 25,000 and 60,000, with a high percentage of monocytes and a small number of abnormal young cells on each examination.

He was admitted to the hospital several times for investigation. No definite diagnosis was ever made. It was felt by some that he had a chronic leukemia in view of the slow increase in the size of the spleen and lymph nodes, while others felt that the unusual blood picture was a reaction to a chronic infection, probably in the lungs, although no definite evidence of pulmonary infection could be found. He was given radiotherapy with slight decrease in the total number of white cells and marked decrease in the number of platelets, resulting in several moderately severe hemorrhages.

On his sixth admission to the wards at the age of 10, there was fever, nausea and vomiting of several days' duration. At this time there were no markedly abnormal physical signs and the red cells numbered 5,800,000, white blood cells 54,000. Dr. Florence Sabin examined the blood smear and reported a large number of monocytes which suggested to her a reaction to a chronic infection rather than a true leukemia. One of the cervical lymph nodes was removed and was found to contain scattered areas of tuberculosis. For several months it was felt that the blood picture was probably a result of the chronic low-grade tuberculosis of the lymph nodes.

During the final year of his life he became sicker and developed many scattered skin infections. The white count during the last 6 months of his life altered considerably with a progressive rise in the total number, reaching 324,000 shortly before his death, 57 per cent polymorphonuclears, 25 per cent lymphocytes, 8 per cent myelocytes, 10 per cent monocytes. The terminal event was the development of an empyema from which a nonhemolytic streptococcus was isolated. At the time of death no satisfactory explanation of the patient's illness during the 3 years that he had been under constant observation was forthcoming. It was felt that, with the terminal very high white count and the progressive anemia, he almost surely had a chronic leukemia.

At autopsy an old, foul-smelling abscess was found in the right lower quadrant in the center of which were the remnants of a ruptured appendix. In addition, there were the changes, both gross and microscopic, usually associated with chronic myeloid leukemia. There was no evidence of tuberculosis.

The final anatomic diagnosis was chronic appendicitis with perforation, chronic retrocecal abscess, and chronic myeloid leukemia.

A case of acute appendicitis 3 years before death with rupture and the formation of an abscess. During these 3 years the patient had a chronic suppurative focus about the appendix, and there was a progressive alteration in the blood picture thought to be, at first, a reaction to chronic infection, but simulating before death chronic leukemia.

Autopsy revealed for the first time this chronic focus. It also revealed the changes on which the diagnosis of chronic myeloid leukemia is anatomically based.

CASE 12.—H. P., Unit 66079. A young American school girl, aged 14 years, was suddenly taken with acute abdominal symptoms which proved to be due to a gangrenous appendix. At the time of operation, the blood showed the usual moderate leukocytosis with the relative increase in polymorphonuclear leukocytes. Although immediate recovery appeared to be satisfactory, the wound remained opened and infected. After 5 weeks the patient was readmitted, complaining of increasing weakness and pallor. Examination of the blood at this time showed a moderate secondary anemia with a decrease in the number of platelets. The white count was 15,000 with 88 per cent of large immature cells. There was a high temperature and a blood culture, as well as the wound culture, showed hemolytic streptococcus. Her temperature rose to 106° F. on the sixth day and she died. Just before death the white blood count in the peripheral blood had dropped to 2400 with many immature forms persisting. The clinical diagnosis of acute leukemia, associated with hemolytic streptococcus septicemia, was borne out by the pathology. The most typical leukemic infiltrations were found in the intraäbdominal lymph nodes and in the liver. There had occurred in the tissue about the abdominal wound and in the cecal mucosa an unrestrained growth of streptoccoccus which completely suppressed a local inflammatory reaction. So far as could be told from the sections, there was no involvement of the regional veins, so that the infection of the blood stream must have occurred through the thoracic duct. It is of great interest that the leukemic lymph glands most evidently involved were those situated along the route of absorption from the abdominal wound.

These last two cases are being presented in detail by Dr. K. R. McAlpin and Dr. B. C. Smith.

Discussion. Until the nature of the leukemias and the leukemia-like states is more thoroughly understood, or until such time as experimental methods are devised for the accurate study of these conditions, as they exist in humans, our only method of approach is by the observation and analysis of clinical material. As previously stated, the cases presented here have been selected from a fairly large group and are presented largely for their clinical interest. Any conclusion that may be drawn from observation of material of this sort is at best indefinite, as it is based entirely on impressions. Exact statements cannot be made. Even the additional information derived in many of these cases from the study of the pathologic material is of only limited assistance. From the point of view of the pathologist, the diagnosis of leukemia rests largely on his definition of the term and is not based on any clear understanding of the nature of the disease. Certain stated requirements must be met to make the diagnosis possible. If these previously stated requirements are met, the diagnosis is accepted. If any of these stated requirements do not exist, another diagnosis must be substituted.

In all of the above cases, infection existed. Coincident with this infection there was a deviation in the white blood cell picture from the normal. In the earlier cases this deviation was relatively mild and transient and can be classified as the leukemoid type of reaction. In others, the infection was considerably more severe and the deviation of the blood picture from normal considerably more striking.

In this particular group, the diagnosis of leukemia could not be definitely made either clinically or anatomically, although that condition was often very closely approximated. A few of the cases satisfied both the clinical and the anatomic requirements for making the diagnosis of leukemia and are classified as such. In each case, there seemed to be a relationship between the infection and the blood picture.

The observation of leukemia and leukemoid blood pictures in close relationship to infection is not new. Several observers have attempted to establish infection as the etiologic agent in acute leukemia. The presence of leukemoid blood pictures in association with progressive tuberculosis has been observed and the existence of true leukemia and progressive tuberculosis has been recorded and is not, apparently, an uncommon combination.

The 3 cases of tuberculosis presented here possessed unusual interest in that the relationship between this infection and the abnormal blood picture seemed to be intimate. Case 5 presented the typical clinical picture of acute myeloblastic leukemia and no other clinical diagnosis was considered. If autopsy had not been performed, this case would undoubtedly have been accepted and recorded as a typical example of this blood disease. Autopsy, however, and study of the microscopic sections of the organs did not uphold the diagnosis of leukemia. Instead, an extensive caseating tuberculosis of the lymph nodes and spleen was discovered. This appeared to be a relatively acute process. It is impossible to do more than suggest that the clinical picture of leukemia may have been dependent upon the presence of this extensive tuberculous infection. Case 6, with its markedly enlarged spleen and very high white count, was accepted clinically as an example of chronic leukemia. The presence of abnormal white blood cells in the smear supported this clinical diagnosis, as did the general course of the disease. The presence of the tuberculosis found at autopsy was not suspected before death and again it is felt that perhaps the unusual blood picture presented by this individual may have been dependent upon this progressive infection. Case 7 presented, during life, many features in common with Case 5. Both died with what was clinically acute myeloblastic leukemia. In the former instance, the diagnosis of leukemia was not upheld by autopsy. In the latter instance, the specified requirements for making that diagnosis were present and that diagnosis was made. Whether or not any fundamental difference existed between these 2 cases cannot be stated. The similarity between them during life was so striking and, as the pathologic difference between the two was dependent solely upon the presence of cellular infiltrations in the latter instance, many who observed these cases felt that they might be variations in degree of abnormal hematopoietic system response to infection and not two different biologic processes.

Considerable speculation followed examination of the microscopic sections in Case 8. The diagnosis of leukemia could not be made, although it was obvious that there had been a profound alteration in the hematopoietic system. The possibility arises that had the infection been slightly less acute and had he lived a few days longer, the microscopic lesions of acute leukemia might have had a chance to develop.

The last 2 cases present a very close relationship between the existing infection and the abnormal blood picture. In both of these cases the diagnosis of leukemia was made before death and confirmed at autopsy. It seems fairly clear that the infection in these 2 instances antedated the leukemic changes in the blood. It is possible, therefore, that the blood picture and the cellular infiltration into the various tissues, both quite typical of leukemia, represent a very unusual response on the part of the hematopoietic system to massive infection. Although it is, of course, possible that there was a simultaneous occurrence of these two conditions, the clinical course and autopsy findings strongly suggest that the white blood cell changes were dependent upon the infection. In both these instances, the requirements of the diagnosis of leukemia are satisfied and it seemed probable that the infection was of considerable importance as an etiologic factor in the alteration of the blood.

The preceding group of cases represent a reaction on the part of the bone marrow to stimulation with an overproduction of young and abnormal white cells.

Depression of Leukopoiesis. The following records are presented as instances of depression of the white blood cell elements rather than stimulation. Depression of the white blood cells is known as leukopenia. Leukopenia is the accepted response in such diseases as typhoid fever, chronic tuberculosis and malaria. Leukopenia during the course of disease, usually associated with leukocytosis, has been observed and its frequently serious prognostic significance appreciated.

For extreme degrees of depression of the granular leukocytes the term agranulocytosis has been employed. This has been observed in association with a variety of conditions. A number of cases have now been collected reporting the occurrence of agranulocytosis following intravenous use of arsphenamin.[1] Several instances of this leukocytic reaction to sepsis have been seen,[2] and this type of blood picture in association with an acute necrotizing infection of the throat has been sufficiently observed and recorded to have become the well-established entity of agranulocytic angina.

As an example of agranulocytic angina the following case abstract is presented:

Case 13.—J. F., Unit 244547. An unmarried American woman, aged 55 years, who had been in relatively good health prior to the onset of the present illness. One week before admission she was suddenly seized with

an acute sore throat associated with fever, chills and extreme prostration. At the time of admission she was stuporous and desperately ill. Temperature, 104° F.; pulse, 120; respirations normal. The physical examination was essentially negative except for a widespread redness of the gums and pharynx. The tonsils were buried and covered with a grayish sloughing membrane. The cervical lymph nodes were very slightly enlarged and not tender. On admission her blood count showed red blood cells, 4,100,000; hemoglobin, 80 per cent. The white cells numbered 1400, no polymorphonuclears being seen. Smears from the gums and from the sloughing membrane were unsatisfactory, showing a variety of miscellaneous organisms with probably a few Vincent's organisms. Culture of the gums and throat revealed both hemolytic and nonhemolytic streptococci, Staphylococcus albus, as well as other organisms. No Bacillus pyocyaneus was observed. Blood cultures remained sterile throughout the course of the illness. In spite of daily transfusions during the 14 days she was in the hospital her daily white blood count never rose above 2000 and only 3 polymorphonuclear leukocytes were observed during this entire time. She died 3 weeks after the onset of the symptoms. At no time was there any evidence of jaundice. At autopsy, a necrotizing, sloughing lesion was found involving the membranes of the mouth, pharynx, larynx and upper trachea. There was a terminal bronchopneumonia. The bone marrow was semifluid and reddish in color. The red blood cell elements appeared to be normally distributed. There was almost complete absence of granulocytes and their precursors. There were no other changes of note.

The same general type of syndrome has been seen here, and has been observed elsewhere, following operative procedures upon the teeth or tonsils.

The following case is an example where this reaction was apparently intimately associated with removal of the tonsils:

CASE 14.—C. B., Unit 73733. A Swedish housewife, aged 47 years, 1 week before admission, had her tonsils removed. The day following tonsillectomy she developed a severe sore throat and a temperature which ranged between 103° and 105° F. until the time of admission. Examination revealed a desperately sick, middle-aged woman with swollen tongue. The pharynx was edematous and covered with a grayish necrotic slough. Her temperature was 105°, rising to 106° F. 5 days later when she died. There was a mild secondary anemia. White blood cells on 4 separate examinations ranged between 400 and 800 per c.mm. At no time were any polymorphonuclears observed. The blood Wassermann was negative. The blood culture remained sterile. At autopsy a necrotizing infection of the pharynx and trachea was found with complete suppression of all cells of the granulocytic series in the bone marrow, as well as in the blood. A great variety of organisms occurred in the slough, including Vincent's organisms, spirochetes, and some of the leptothrix group.

In addition to the group of cases that conform in all respects to the accepted description of agranulocytic angina, a large number of interesting variations have been observed. Similar cases have, in most instances, been previously reported in the literature. There have been several reports to date of this type of response in individuals receiving antiluetic treatment (1) and one instance of this has been observed here. In addition, this type of bone marrow depression has been observed with several different types of infec-

tious diseases. These include cases of localized infection as well as general septicemia. Although the Bacillus pyocyaneus was at one time thought to be a possible factor in this white cell depression, subsequent case analyses have shown that this organism is rarely present. One case has been observed in the wards of this hospital in which this organism was apparently the etiologic agent. In this instance the lesion was localized and superficial, in a location that permitted prompt local therapy, with a resulting disappearance of the lesion and a return of the blood picture to normal.

CASE 15.—S. W., Unit 825352. A graduate nurse, married, aged 45 years, with irrelevant past history who, 5 days before admission, developed sore throat and fever. At the same time she noticed a sharp pain in the rectum. The throat continued sore and the pain in the rectum increased. The temperature on admission was 104.8° F. Examination revealed an acutely ill, middle-aged woman. Her tonsils were large and boggy with occasional spots of whitish exudate. Her throat was only moderately inflamed and no ulcers were observed. Near the anal orifice on the left side were 2 shallow ulcerations covered by a grayish slough. Culture of the throat revealed a variety of organisms. Culture of the anal ulcers grew out almost pure Bacillus pyocyaneus. On admission the red count was normal, white blood cells were 1700; polymorphonuclears, 16 per cent; lymphocytes, 75 per cent. It was felt that the relative agranulocytosis was probably related to the anal ulcers and not to the mild pharyngitis. Treatment of the anal ulcers with Lugol's solution and dilute tincture of iodin resulted in prompt healing, with return of temperature to normal on the third day and rapid increase in the polymorphonuclears, the total white cells reaching 2400 with 48 per cent polymorphonuclears at the end of the first week, and 7500 white cells with 70 per cent polymorphonuclears at the end of the second week at which time she was discharged. Blood cultures on admission remained sterile. She has subsequently returned to work without symptoms of any kind.

The agranulocytic type of blood picture has been observed in association with a rapidly spreading staphylococcus carbuncle of the face.

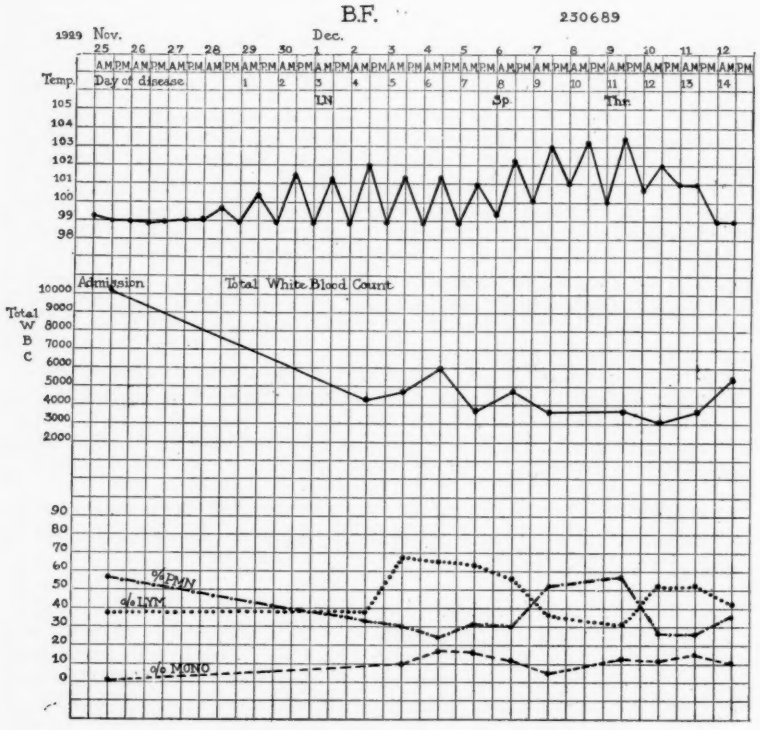
CASE 16.—F. F., Unit 79835. A man, aged 76 years, came in complaining of an infection on the right cheek of 4 days' duration. On admission his temperature was 101.2° F., pulse 102. The mouth and throat were normal. On the right cheek was a small indurated furuncle. Red blood cells, 4,000,000; hemoglobin, 80 per cent; white blood cells, 1300; polymorphonuclears, 0; lymphocytes, 94 per cent; monocytes, 6 per cent. In spite of treatment of the furuncle on the cheek and several transfusions, the infection spread rapidly, involving half of the face and neck, with beginning gangrene. His temperature rose to 104° F. on the fourth day, and he died on the sixth day. At no time, even immediately after transfusions, were any polymorphonuclears seen in the blood. Blood cultures were sterile. Cultures from the cheek grew out a pure culture of hemolytic staphylococcus aureus.

A group of 7 cases that presented strikingly similar clinical pictures have been observed here during the past year. These have been collected and published as examples of extreme depression in the granulocytic cells of the blood in association with a transient,

relatively mild pharyngitis.[3] It is of interest that all the cases of this group, with but one possible exception, recovered promptly with return of the blood picture to normal. A typical example of this group is presented here.

CASE 17.—B. F., Unit 230689. A Jewish subway guard, aged 40 years, was admitted to the medical wards for study of a mild hyperthyroidism. His admission blood count showed 4,700,000 red blood cells, 10,300 white blood cells; 56 per cent polymorphonuclears; 37 per cent lymphocytes, 7 per cent monocytes; no abnormal cells were seen. For the first 3 days his

CHART II.



LN, appearance of enlarged lymph nodes. Sp, appearance of spleen; Thr., appearance of pharyngitis.

temperature remained normal. On the 4th day it began to be progressively elevated. For the next 2 weeks the temperature was spiking in character, being normal in the morning, rising in the evening to between 102° to 103°, reaching 104.2° F. at one time. There were no symptoms with the initial rise in temperature and no physical signs to explain it other than a very slightly reddened throat. After a week of this unexplained fever moderate enlargement of the posterior cervical lymph nodes was noted. On the 4th day of this acute illness the red blood count was found to be normal, the white blood cells had fallen to 4000; 33 per cent polymor-

phonuclears. Frequent white blood counts during the next 10 days are shown in the accompanying chart. (Chart II.) On the 10th day of this acute illness the patient was still without symptoms and there was no change in the appearance of the throat. The glands were thought to be larger and were described as soft and slightly tender. The tip of the spleen could just be felt on deep inspiration. It was not until the 12th day that his throat was noticed as being more diffusely reddened than previously, and on the day following, small, white, round, superficial ulcerations, resembling Staphylococcus albus colonies on a blood plate, were seen. With the appearance of these, the temperature began falling, reaching normal on the 16th day. This was followed by rapid clearing of the throat lesions, prompt regression of the lymph nodes, and a rapid return of the blood count to normal.

The agranulocytic type of blood picture has also been observed in association with descending infection of the respiratory tract with terminal pneumonia and empyema.

CASE 18.—J. S., Unit 70607. A young boy, aged 19 years, came in with a history of a severe sore throat beginning 1 week before admission. The day following the onset of the sore throat, a peritonsillar abscess was incised with transient relief of the pain. Three days before admission he became much worse, with high fever, pain in the chest, and a cough productive of blood-tinged sputum. Temperature, 105° F.; pulse, 132; respirations, 38. Examination revealed a desperately sick young man. There was a sloughing area on the anterior part of the right tonsil and the physical signs of consolidation of the left lower lobe. The next morning the physical signs changed somewhat and fluid was suspected. Thoracentesis revealed 800 cc. of thin, yellow, foul-smelling fluid which contained a mass of organisms from which hemolytic streptococcus, pneumococcus IV, and various anaërobes were recovered. He became rapidly worse and died 24 hours after admission.

His red blood count was 4,000,000; hemoglobin, 75 per cent; white blood cells, 100; polymorphonuclears, 3 per cent. There were 58 per cent of typical small lymphocytes and 39 per cent large immature cells thought to be myeloblasts.

It seems probable that this case originally represented a peritonsillar abscess. Following incision gangrene of the lung developed with subsequent empyema. The blood picture showed marked depression in the number of mature polymorphonuclears with a very high percentage of immature granulocytes. Some felt that this blood picture represented an acute leukemia, but most of those who saw the patient and the blood smears thought that the leukocytic picture represented a severe agranulocytic type of reaction to an overwhelming infection with an attempt on the part of the bone marrow to put out cells. Autopsy was not obtained.

Another variation that has been observed is illustrated in the following cases of hemolytic streptococcus infection with terminal hemolytic streptococcus septicemia:

CASE 19.—I. R., Unit 84664. An American graduate nurse, aged 37 years, who had a sore throat and tonsillitis during the 10 days before admission. During the 2 days before she came in, her temperature rose

rapidly, reaching 104° F., and there was marked prostration. On admission she had a temperature of 106°, pulse 130, and she was obviously *in extremis*. Over the entire body there was a diffuse erythematous rash which faded on pressure. Her tonsils were deep red, swollen, and each was covered with a whitish-gray slough. The examination was otherwise negative. The red count was normal; white blood cells, 150; polymorphonuclear, 0. The blood culture grew out a heavy growth of hemolytic streptococcus. Her temperature rose rapidly to 108° and she died.

Autopsy revealed a fulminant throat infection with invasion of the blood stream by hemolytic streptococcus. No metastatic foci were found. The bone marrow was deep red and contained abundant mature and immature red blood cells, but almost no cells of the granulocytic series.

CASE 20.—A. R., Unit 266942. An elderly Irish housewife came into the surgical ward complaining of having burnt the fingers of one hand 48 hours previously. During the preceding 2 months she had felt slightly tired but was otherwise quite well. The original burn was not particularly severe but had been followed by rapidly progressive inflammation of the dorsum of the hand. On entrance she was acutely ill with a temperature of 104° F. and there was an acute, rapidly spreading cellulitis of the hand and an associated lymphangitis and lymphadenitis. There were no petechiæ. Admission blood count showed a normal number of red cells but only 480 white blood cells with no polymorphonuclears. The local infection spread rapidly. Hemolytic streptococcus was recovered from it and from the blood, and the patient died 3 days after admission. On the day before death her white cells numbered 520 and there were still no polymorphonuclears.

CASE 21.—B. M., Unit 70314. An American, aged 65 years, came in complaining of frequency and nocturia for 2 years with complete anuria for 10 hours. On admission he was found to have an enlarged prostate. A suprapubic prostatectomy was done in two stages and except for rather violent postoperative rises in temperature, his convalescence following the second operation seemed entirely satisfactory. His blood count during this entire time was normal, except during the febrile reaction to the first operation, when the total white cells numbered 31,000; 85 per cent polymorphonuclears. Two weeks after the second operation the white blood cells were 7200, polymorphonuclears, 82 per cent. After several days of normal temperature and with beginning closure of the abdominal wound, he was allowed in a chair for several days, but developed, a week later, what was apparently a mild bronchitis. This promptly cleared and again convalescence was satisfactory. Then he developed an acutely sore throat with a rapid rise in temperature to 105° F. White blood cells on this day were 3800; polymorphonuclear, 0; 95 per cent lymphocytes, 5 per cent monocytes. He became rapidly worse, his temperature rose to 106° F., and 3 days after the onset of symptoms he died. Blood cultures grew out hemolytic streptococcus in both flasks. Cultures of the throat, which was infected and acutely inflamed, revealed a large number of hemolytic streptococci. Autopsy was not obtained.

This case was of particular interest in that the entire terminal illness occurred while the patient was under observation in the ward. Previous blood counts had been done. In these a normal response to infection had been observed. While under observation and while convalescing satisfactorily from the prostatectomy he was infected with unusually virulent hemolytic streptococcus. This

infection was rapidly progressive and was associated with an extreme depression of the leukocytes.

Discussion. In the last group of unusual white blood cell pictures there has been a selective depression of the granular elements. This blood picture conforms to the accepted definition of agranulocytosis. In all of these cases infection has existed. Apparently coincident with this infection there has been a deviation of the blood picture from the normal.

The question of the etiologic importance of the infection in the production of this blood picture has not been settled. Some observers believe that the infection, present in nearly all of these cases of agranulocytosis, is secondary to a primary bone marrow depression of unknown etiology. Clinical reports are cited to substantiate their views. One of the most recent and best studied is the case presented by Roberts and Kracke.[4] Other authors think that agranulocytosis is a peculiarly selective type of bone marrow response to a wide variety of toxic agents.[5] It is still an open question and one that will probably not be definitely settled until enough accurate clinical data have been obtained and analyzed, or until such time as a similar syndrome may be studied in the laboratory.

Observation of our cases has been of little assistance in settling this question. In our opinion, however, several of these cases offer clinical evidence in support of the impression that the infection was of primary importance in the production of this syndrome. In this connection, Case 15 was of particular interest in that the patient's infection was in a location and of a type that permitted immediate local treatment. With the regression of the infection there was a prompt return of the blood picture to normal and progressive improvement in the patient's general condition. In Case 21 previous blood counts had shown a normal response, but with the advent of the new and virulent hemolytic streptococcus infection, the agranulocytic type of blood picture developed.

We realize, in this group, as in the previous group, the futility of drawing definite conclusions from the observation of limited clinical material. We believe, however, that these patients as we have seen them strongly suggest that the presence of a toxic agent within the body, whether this be a relatively simple chemical such as neoarsphenamin or the complicated products of an infection, may be of considerable importance in the production of this selective bone marrow depression.

Conclusion. Two groups of cases are presented in which there has been an unusual white blood cell picture. In the first group, stimulation of the leukocytic elements produced various strange blood pictures, several of which were indistinguishable from leukemia. In the second group depression of the granular cells resulted in agranulocytosis. In all these cases infection existed. The pos-

sible relation between the presence of the infection in the body and the coincident deviation of the blood picture from the normal is discussed.

BIBLIOGRAPHY.

1. Farley, David L.: Depressed Bone-marrow Function from the Arsphenamins (Including a Type of So-called Agranulocytosis), AM. J. MED. SCI., 1930, **179**, 214.
2. Blumer, George: The Agranulocytic Blood Picture in Conditions Other Than Angina, AM. J. MED. SCI., 1930, **179**, 11.
3. Thompson, William P.: Leukopenia Resembling Agranulocytosis with Recovery, AM. J. MED. SCI., 1930, **180**, 232.
4. Roberts, Stewart, R., and Kracke, Roy R.: Agranulocytosis, Report of a Case, J. Am. Med. Assn., 1930, **95**, 780.
5. Aubertin, Charles, and Levy, Robert: L'Agranylocytose et les syndromes Agranulocytaires, Arch. des mal du cœur, 1928, **21**, 369.

PNEUMOPERITONEUM IN THE TREATMENT OF TUBERCULOUS ENTEROCOLITIS.

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TUBERCULOUS disease of the intestines is far more frequently a complication of pulmonary tuberculosis than is generally realized. Schwatt and Steinbach[1] estimate that tuberculous ulcers of the intestines occur in from 60 to 90 per cent of cases of fatal phthisis. Walsh[2] found 76 per cent and Engelsmann[3] 92.6 per cent intestinal ulcerations in patients dead of pulmonary tuberculosis. It is evident from these data that the majority of our far-advanced pulmonary cases acquire this condition some time during the course of the disease. Still it is generally admitted that no such high percentage of patients with far-advanced pulmonary tuberculosis is treated for intestinal tuberculosis. Steinbach[1] reports that of 127 cases of intestinal tuberculosis, in which definite ulceration was found at necropsy, no diagnosis in 78 (61.5 per cent) was arrived at during life because of the absence of clinical symptoms referable to the intestinal tract. It may be reasonably presumed that a similar state of affairs prevails in all tuberculosis institutions throughout the country. Searching for reasons why no adequate attention is given to this most frequent complication of pulmonary tuberculosis, the following points seem to be obvious: (1) Lack of diagnostic consciousness; (2) improper interpretation of symptoms and signs; (3) incomplete diagnostic investigation; (4) asymptomatic forms of intestinal tuberculosis.

Stewart[4] aptly says that if we are not aware of serious trouble until the well-known late and grave symptoms of intestinal tuber-

culosis, such as diarrhea with foul-smelling stools, emaciation, tenderness, pain and sudden collapse, develop, we are just where our grandfathers were with consumption half a century ago.

Onset and Symptoms. The onset of tuberculous enterocolitis simultaneously with the pulmonary process is comparatively rare. In the overwhelming majority of cases the onset follows several months or years of observation of the pulmonary disease. It must be kept in mind that macroscopic ulceration, hyperplasia or cicatrical stenosis are later changes in the course of tuberculosis of the intestines. These changes are preceded by stages from a solitary tubercle localized in the mucosa, or the lymphatic tissue of the submucosa, to conglomeration of tubercles and microscopic ulcerations. Furthermore, such conglomerate tubercles distributed in different portions of the intestinal tract may persist without ulceration for a long time. There is no parallelism between the extent of intestinal involvement and the intensity of symptoms. Minor pathologic changes limited to a small portion of the intestine may cause severe symptoms and *vice versa*. Symptoms such as anorexia, aversion for food, fullness after eating a small amount of food, distress after eating, sour stomach, heart burn, eructation, nausea, constipation, abdominal pains aggravated by eating and relieved by fasting, may be observed during the early developmental stages of the disease. At the same time, it is noted that the patient is not doing well, though the pulmonary condition seems to be stationary or improving. Rise in temperature, malaise, failure to gain or rapid loss of weight otherwise unexplained and nervous irritability often accompany the onset.

It was suggested by Paterson[5] that starvation for 48 hours caused the disappearance of symptoms, particularly the fever; in these cases this is used to determine whether the symptoms have their origin in the lungs or in the gastrointestinal tract. Diarrhea is not characteristic of ulceration in the large intestine. It may be present in cases of ulceration in the large or the small intestine or both. It is usually indicative of extensive involvement. Constipation should not be taken as a sign of ulcer formation in the small intestine, nor constipation alternating with diarrhea as indicating ulceration in the small and the large bowel. Pain on deep palpation is suggestive of ulceration, but the point of maximum tenderness does not necessarily coincide with the site of maximum involvement. Rigidity of the abdominal wall is indicative of disease of the serosa.

The absorption of tuberculotoxins from active pulmonary foci undoubtedly may cause diminished hydrochloric acid secretion in the stomach with functional impairment in other parts of the gastrointestinal tract, resulting in anorexia, epigastric distress, eructation, nausea, vomiting, gas distress, flatulence, colic, irregular bowel action, loss of weight and increased nervous irritability. If such symptoms persist or become worse in spite of adequate treat-

ment of the pulmonary process, a diagnostic survey of the case for intestinal tuberculosis should be urged. It is safer to be overzealous in the detection of early intestinal tuberculosis than to discover it too late. The deficit in the defense of the body due to intestinal tuberculosis should be recognized and eliminated at the earliest possible time. Naturally, nontuberculous diseases of the gastrointestinal tract, such as peptic ulcer, nonspecific enterocolitis, malignancy, amyloidosis and digestive disturbances due to dietetic errors, must be differentiated.

Diagnosis. It is possible to establish the diagnosis of intestinal tuberculosis on the basis of symptoms and physical findings. Still it seems advisable that corroborative evidence be obtained by means of Roentgen ray in all cases, with manifest as well as suspected intestinal lesions. Smithies, Weisman and Fremmel[6] are of the opinion that "no person in whom pulmonary tuberculosis is proved or suspected can be considered as having been properly examined without a roentgenologic study of the alimentary tract." A positive Stierlin sign, that is, failure of the barium meal to remain in the cecum and ascending colon 6 or 7 hours after ingestion of the progress meal, while the terminal ileum and the transverse colon are filled, indicates infiltrative or ulcerative tuberculosis of the cecum or the ascending colon. This phenomenon is due to increased irritability and hypermotility of the involved areas. Nontuberculous inflammatory conditions causing an absence of the normal shadow are rarely localized within 12 inches proximally or distally to the ileocecal valve. A negative Stierlin sign does not exclude tuberculosis of the cecum or ascending colon. A localized or generalized hyperperistalsis resulting in "filling defects" may be present in very early as well as in very extensive lesions. Hypertrophic circular scars may cause easily demonstrable partial obstruction. Brown and Sampson[7] point out, that if the site of the ulceration is in the small intestine, as a result of hyperirritability and spasm, a temporary stasis and dilatation of the proximal segment develop. Barium meal should never be omitted whenever the question of a possible intestinal tuberculosis arises. Deformities due to adhesions, or malignancy of abdominal organs, syphilis and nontuberculous inflammatory disease of the intestines must be excluded.

Laboratory methods afford little aid in diagnosis, with the exception of positive findings as to blood in the stools that is suggestive of intestinal ulceration. Erickson[8] reports intestinal bleeding in 13 per cent of his cases, in 6 per cent of which there was a real hemorrhage.

Even using utmost care in evaluating clinical, roentgenologic and laboratory data, it may be impossible to arrive at a correct diagnosis. (1) Because our present-day methods have their limitations, as emphasized by Steinbach,[9] stating that in 52 per cent of his 67 cases of far-advanced pulmonary tuberculosis, in whom a com-

parative study of the clinical and postmortem findings was made, the roentgenologic signs considered diagnostic of intestinal tuberculosis were highly unreliable. (2) Because there are cases of this complication without pain or any other subjective manifestation, cases that are never recognized as such unless on the postmortem table.

The prognosis of intestinal tuberculosis is not necessarily hopeless, even if it is accompanied by far-advanced pulmonary tuberculosis. Complete healing of exudative and ulcerative lesions was observed in animal experiments, roentgenologically, clinically and on the postmortem table. We think that with the available diagnostic and therapeutic facilities a therapeutic pessimism or negativism is not more justified than the omission of adequate sanatorium treatment in pulmonary forms.

Treatment. If the plea of the phthisiologist for early diagnosis of pulmonary tuberculosis is reasonable and justified by the far higher percentage of recoveries in early than in advanced cases, it is only logical to extend a similar plea to the phthisiologist concerning intestinal tuberculosis. The cure of any form of tuberculosis lies in its early diagnosis. The attitude of Stewart[4] deserves wide attention and propagation. He says: "In some cases when symptoms begin lesions have already become gross. To wait for symptoms is to wait months beyond a time when a diagnosis can be made by the barium meal. The only proper method is to anticipate symptoms, discover the disease before it is gross enough to show them, and make the diagnosis without them." Besides protection of the abdomen and decrease of exercise, if necessary to absolute bed rest, the following methods are available for the treatment of intestinal tuberculosis: (1) Prophylactic, (2) dietetic, (3) medicinal, (4) ultraviolet and Roentgen ray irradiation, (5) surgical and (6) pneumoperitoneum.

Kantor[10] emphasizes the importance of prophylaxis in the treatment of secondary intestinal tuberculosis. He offers four measures for this purpose: (1) The avoidance of swallowing tuberculous sputum. The finding of tubercle bacilli in 90 per cent of the stools of patients with open tuberculosis of the lungs highly justifies this standpoint. (2) Administration of dilute hydrochloric acid in the subacidity cases. This latter suggestion is supported by the investigations of Rolleston[11] that show that ulcers extend higher up in the intestinal tract of patients suffering with anacidity than in cases with normal acidity. (3) The prevention of intestinal stasis and the eradication of all forms of constipation. Any factor that would prolong the sojourn of fecal material in the terminal ileum and cecocolon, which is normally about 3 to 5 and 18 to 33 hours respectively, must be eliminated. The prevention of fecal retention will decrease the opportunity for tuberculous infection. (4) Prompt and comprehensive survey of every tuberculous dyspeptic.

It is erroneous to force amounts of food overstepping the patient's tolerance in gastrointestinal subcompetency due to tuberculosis. Food given over tolerance will not be utilized and will cause harmful irritation. The optimum diet is the minimum maintenance diet based on basal caloric requirements. Kantor[10] recommends for routine feeding the Schmidt intestinal test diet containing proteins, carbohydrates and fats in well-balanced ratio. Meals must be small in bulk, cellulose-free, of smooth consistency, thoroughly strained, composed of easily assimilable foods not causing fermentation. When diarrhea is pronounced liquid diet is indicated. By bland diet irritation of the inflamed surface and ulcerated areas is avoided, and thus cramping pain and diarrhea may be alleviated. Milk should be used cautiously and preferably in small quantities, because its undigested curds may irritate the bowels and cause diarrhea. It may be said, that in general, dietetic treatment alone is not an adequate therapeutic procedure. During more than a year of experience with the Sauerbruch, Hermannsdorfer, Gerson diet we found that patients with gross intestinal tuberculosis tolerate the "salt-free" diet very poorly.

In case of diarrhea intravenous injection or oral administration of calcium, oral medication with bismuth, tannic acid, atropin and opium preparations may be given. In some cases bowel irrigations with physiologic saline solution or with appropriate solutions of astringents and antiseptics as tannic acid, silver nitrate and mercurochrome may give relief.

Excellent results were observed by several investigators after treatment with natural and artificial sunlight. Brown and Sampson[7] report that of the group treated by ultraviolet irradiation 65 per cent improved and 40 per cent were free of symptoms after treatment for 1 month; after 2 months' treatment 70 per cent were improved and 60 per cent became symptom-free, all patients were improved and 85 per cent had lost all symptoms after 6 months' treatment. Bacmeister[13] saw favorable effects upon intestinal tuberculosis from the use of Roentgen ray irradiation.

Valuable information as to the surgical management of intestinal tuberculosis was brought out by Smithies, Weisman and Fremmel.[6] They state that no surgical operation should be performed in patients with rapidly progressing toxic pulmonary lesions complicated by extensive intestinal involvement without any reparative tendency. The physical and Roentgen ray findings of the abdomen are marked, and ischiorectal abscess and exudative peritonitis are frequent complications in these cases. Early exploratory laparotomy and removal of the diseased portion of the intestine under local or spinal anesthesia is recommended by them in two groups of patients: (1) In mildly active or quiescent pulmonary tuberculosis accompanied by dyspeptic disturbances of rather mild and irritative character; also constitutional symptoms are absent, as well as

evidence of gross anomalies on abdominal examination; (2) in patients with quiescent or intermittently active, extensive pulmonary processes, in which intestinal tuberculosis develops in the later course of the thoracic disease. There is usually definite pain, diarrhea, malnutrition, dehydration, prostration; the physical and Roentgen ray findings indicate well-localized lesion of mild degree in the terminal ileum, cecum or the colon. Archibald[12] reports also favorably on the surgical treatment of intestinal tuberculosis.

TREATMENT BY PNEUMOPERITONEUM. Pneumoperitoneum with oxygen was given in 44 of our cases. The inflations were done between breakfast and lunch, preferably not too close to the noon hour, to avoid possible interference with the patient's meal. No special preparation is necessary except the evacuation of the bladder just before operation. Enemas or cathartics are not used, (1) because of the discomfort and weakness, and (2) because there is no accumulation of fecal material in the irritated hyperperistaltic intestines. In patients with severe cough an adequate dose of codein is given 1 hour before treatment. The best site for injection is three fingers' breadth below and to the left of the umbilicus, although in cases where the left side is used too often fibrosis and adhesions develop, preventing the smooth introduction of the needle, the same level can be taken on the right side. Injury to the deep epigastric artery, mesenteric vessels and intestines causing embolism, hemorrhage, peritonitis, furthermore the danger of peritoneal shock, are so remote that they do not militate the least against the use of this procedure. No occurrence of subcutaneous emphysema or collapse due to sudden absorption of the injected oxygen was seen in this series.

One per cent novocain is used for infiltration of the abdominal wall, particular attention being given to the peritoneum to avoid shock. By elevating a skin fold between thumb and index finger a small skin incision is made to aid smooth insertion of the Floyd-Robinson needle. The size and shape of this needle facilitates introduction into the abdominal cavity as well as the inflation of oxygen from a standard pneumothorax apparatus. The direction of the needle should be diagonal, pointing upward and toward the midline, to ensure perfect closure and prevent the back flow of oxygen under increased abdominal pressure. Only exceptionally do we find patients with heavy abdominal walls, that necessitate a perpendicular perforation, because the diagonally inserted needle would not reach the peritoneal cavity. Manometer readings are taken following insertion of the needle, though it is well known that the manometer does not have such important and indispensable rôle in pneumoperitoneum as in artificial pneumothorax treatment. The intraädominal pressure is neutral in untreated cases. Since there is not any initial intraäbdominal negative pressure, the operator must get his orientation from lack of resistance when the

needle enters the peritoneal cavity. Slight positive pressure, amounting to from 0.5 to 1 cm. of water, was very rarely seen in patients without previous treatment. It can be said that the manometer is not as sensitive an indicator of the air content of the abdominal as of the pleural cavity. Positive pressure and oscillations appear usually after the inflation of 300 to 500 cc. of oxygen. Still in some instances the oscillations as well as the appearance of positive pressure are not evident even after 1000 cc. of oxygen were injected. In such cases the disappearance of liver dullness after the injection of 300 to 400 cc. of oxygen or the subjective feeling of the patient will serve as useful guides as to the presence of air in the peritoneal cavity. The right hypochondriac area can be easily percussed by "palm" percussion by the operator himself. This method may often give us early information of a correctly performed inflation before any sensation is indicated by the patient. A tympanitic percussion note over this area following injection of more than 500 cc. of oxygen is absent only in cases where the space between the liver and the overlying abdominal wall is obliterated by adhesions, as we had the opportunity to observe in some of our cases. Two other interesting phenomena were recorded: (1) That in some instances positive pressure (+3 and +4) following the injection of from 750 to 1200 cc. of oxygen disappeared after few respirations, though the absence of liver dullness, distention and loud tympanitic percussion sound of the abdomen and subjective feeling of the patient indicated the presence of oxygen; (2) in 3 patients a paradoxical oscillation in the manometer, that is, a decrease of the pressure by about 1 cm. of water on deep inspiration and a return to its original level on expiration was seen after the inflation of considerable amounts (800 to 1000 cc.) of oxygen. Normally the positive pressure is increased on inspiration and decreased on expiration. The flow of oxygen is slower than one is used to seeing in giving artificial pneumothorax, due to the absence of the suction effect of negative pressure. To increase the speed of flow it is advisable to elevate the second bottle (containing water).

An early sharp rise of positive pressure with too wide oscillations should be considered a sign of adhesions. No unduly large amounts of oxygen should be forced into the abominal cavity, in such instances, to avoid undue tension and discomfort. The subjective feeling of the patient, the distention of the abdomen and increased intensity of tympanitic percussion sound are far better guides in controlling the amount of oxygen injected than the manometer. Great variations in the sensory reaction to the inflations were met with in different patients. The sensibility of the patient, the size of the abdominal cavity, presence of tuberculous peritonitis and adhesions, limitation in motion of the diaphragm and the extent of the pulmonary disease are the main factors in this respect. The

extent of the intestinal involvement in itself has no great significance, if any, in this connection. Patients with extensive involvement were given large amounts of oxygen without discomfort, while several cases with less extensive disease had marked complaints due to distention following the inflation of comparatively small amounts of oxygen. In some patients with severe bilateral pulmonary tuberculosis the sudden rise of the diaphragm induced by the injected oxygen caused considerable dyspnea. There is usually no indication of fullness or pain at the level of the diaphragm or in one of the shoulders when less than 300 cc. of oxygen are given. Indication of such sensations is more frequent after 500 cc. In all but 2 instances diaphragmatic or shoulder pain were indicated when more than 1000 cc. was introduced. Where tension and discomfort were minimal the patient was allowed to walk back to his room, and his prescribed daily routine was not changed because of the pneumoperitoneum. Still in the majority of cases it was necessary to relieve the discomfort due to tension or shoulder pains by elevating the foot of the bed. This simple measure by shifting the oxygen from below the diaphragm toward the pelvis, a change not unlike the shifting of the air bubble in the carpenter's level, proved to be successful in practically all cases where it was used. In 24 to 48 hours these patients resumed a normal position without being conscious of any abdominal distress due to treatment. This can be explained by the fact that there is a rapid absorption of the injected oxygen, with a complete disappearance of it in a few days. We had the opportunity to observe that in some patients the absorption rate diminished with the increasing number of inflations.

The amount of oxygen should be adapted to the requirements of the individual case, the chief criterion being the subjective response of the patient during operation. The abdomen should be rather under than overinflated because pressure or tension may become more noticeable to and discomforting for the patient when he leaves the operating table or tries to occupy a semirecumbent position in his bed. The largest amount of oxygen injected was 1500 and the smallest amount 150 cc. Often the amount of oxygen was gradually increased until about 1000 cc. was reached, and then the patient was carried on such doses as long as it was deemed necessary. It was noted that patients required inflations at certain intervals, the length of which varied from 1 to 2 weeks, rarely longer, and only in 1 instance as short as 3 days. In Cases 20, 31, 35 and 36 the inflation tolerance, that is, the intraäbdominal capacity, markedly decreased as the course of treatment progressed. In Case 20 the oxygen was reduced from 1000 to 500, in Case 31 from 1000 to 300, in Case 35 from 1000 to 600 and in Case 36 from 1000 to 150 cc. This decreased intraäbdominal capacity is undoubtedly due to developing adhesions.

Complaint of nausea, following and apparently caused by the

inflation, was met with only once. In 1 of our cases in whom the oxygen injection was given during menstruation severe cramping pains developed in the lower part of the abdomen; in a patient having taken several inflations the injection of 950 cc. of oxygen was followed by a feeling of tightness in the heart region, at the same time the abdomen appeared dilated and the position of the diaphragm was found to be high. In Case 20, at the thirteenth inflation, the amount of oxygen having been reduced from 1000 to 500 cc., when the patient returned to her room she felt "something snap" below the ribs on the right side, had excruciating pains at the level of the diaphragm that did not improve on elevating the foot of the bed and gradually disappeared in 3 days. It may be reasonably supposed that the reflex nausea, irritation of the female genital organs in menstrual congestion, undue upward displacement of the diaphragm with cardiac embarrassment and stretching or separation of the adhesions were caused by unduly high intraäbdominal pressure. Such disagreeable incidents can be prevented by avoiding the menstrual period and not forcing too large amounts of oxygen into the abdominal cavity.

Expectoration, with or without increased cough, may be increased during the first 2 days following inflation. This is due to the elevation of the diaphragm that can be visualized under the fluoroscope or on the roentgenogram. If abdominal tightness or shoulder pains are present the cough is usually decreased, since the patient is automatically trying to avoid discomfort resulting from cough.

It is conceivable that the elevation of the diaphragm may exert a favorable influence upon the healing of the pulmonary process by limiting the excursions of the diaphragm and by decreasing the intrapleural negative pressure, which, in turn, will increase the blood supply of the pulmonary tissue. Still it is known that the injected oxygen is absorbed in 2 to 3 days. Therefore, an indirect curative effect upon the pulmonary process may be discounted or considered irrelevant in face of the fact that inflations are repeated at 1 or 2 weeks or longer intervals, and thus the high level of the diaphragm is maintained only during a small fraction of the treatment.

The greatest upward displacement of the diaphragm was observed in Cases 33 and 37. In the first, pneumoperitoneum was instituted following a block of the right phrenic nerve, and in the second case, after bilateral phrenic paralysis was surgically established. It is remarkable how well and easily this latter patient adapted herself to the changed respiratory mechanism of her body. Another unusually interesting patient was Case 36, who was treated simultaneously by bilateral artificial pneumothorax and pneumoperitoneum, taking 400 cc. of air on each side of the chest and 500 to 1000 cc. of oxygen intraperitoneally without manifest discomfort or respiratory embarrassment.

The mechanism of the effect of injected oxygen upon the intestinal

lesions is not exactly known. Of the different hypotheses two seem to be most compatible with the results obtained: (1) Oxygen increases cell activity in all body tissues, effecting a better local and general immunologic response; (2) injected oxygen due to its chemical properties and increased intraäbdominal pressure will cause irritation of the peritoneum and intestinal serosa with subsequent hyperemia. A decrease in the peristalsis following oxygen inflations was noted in the majority of our cases. By these accomplishments we are approaching the ideal aimed at in the treatment of any form of tuberculosis, that is, possible maximum immobilization with improved nutrition and immune body supply to the diseased tissues. Bainbridge[14] used oxygen injections following abdominal operations and for the treatment of certain types of tuberculous peritonitis with a view of stimulating tissues, preventing the extension of inflammation, causing increased leukocytosis and phagocytosis, destroying the germs or diminishing their virulence and neutralizing their toxins. Burkhart[15] found in animal experiments that oxygen is an irritant to the peritoneum and is able to increase the reactive capacity of same by bringing about leukocytosis. The symptomatic relief may be immediate or following inflation in 24 to 48 hours. In some cases it may last for 2 to 3 weeks or eventually for a few months in spite of the fact that oxygen is absorbed from the peritoneal cavity in 2 or 3 days. This circumstance indicates that favorable changes are not so much due to the increased abdominal pressure as to the hyperemia that persists after the absorption of oxygen. The relief of the patient with advanced pulmonary tuberculosis from anoxemia and the action of oxygen as a mild cardiac and respiratory stimulant may explain the immediate euphoria seen in some of our patients independently of the local effect of oxygen.

Oxygen or air injection has been used for the treatment of tuberculous peritonitis since 1893. Of the more recent investigators Stein,[16] Mattick[17] and Gilbert[18] consider pneumoperitoneum as a valuable method of treatment for this condition. Laney[19] reports 3 patients with tuberculous enterocolitis, 2 of whom showed great symptomatic relief following pneumoperitoneum. In 1 diarrhea and abdominal pain were relieved by two inflations; in the other, a patient in preterminal stage, 400 cc. of oxygen decreased the diarrhea and greatly relieved the abdominal distress. He states that pneumoperitoneum is such a simple and safe procedure that it should be used more frequently on account of the relief that it affords to patients suffering with intestinal tuberculosis. A similar opinion was expressed by Hayes,[20] with the addition that in early cases it may be instrumental in effecting a cure. He reports that in the 4 cases of ulcerative intestinal tuberculosis, accompanying far-advanced pumonary tuberculosis, that were treated by diet, intravenous calcium injections and medication without relief, the appe-

tite improved and the diarrhea was reduced from 10 to 20 movements a day to 2 or 3 by oxygen inflation of the abdomen.

This paper is based upon the observations in 44 cases of intestinal tuberculosis treated by pneumoperitoneum during the last 2 years. This number represents a comparatively small percentage of patients with tuberculous enterocolitis in this institution, considering the fact that almost 50 per cent of our admissions are made up of far advanced pulmonary cases. Only patients not showing satisfactory response to dietetic and medicinal treatment were included in this group.

The following brief summary gives detailed information as to the type of case, symptomatology, duration of treatment and end results. The diagnosis was established on the basis of clinical and roentgenologic findings.

Case Reports. CASE 1.—F. H., aged 53 years, white, male. Far-advanced pulmonary tuberculosis involving all lobes, of 6 years' duration. Gastrointestinal symptoms: Lack of appetite, nausea, vomiting, abdominal pains, diarrhea, blood in stools for 1 month. January 23, 1929: 400 cc. oxygen; February 15: 800 cc. Much relieved after first treatment. All symptoms gone following second inflation. Symptom-free for 2 years.

CASE 2.—W. R., aged 27 years, white, male. Far-advanced pulmonary tuberculosis, involving both upper and lower lobes for 1.5 years. Gastrointestinal symptoms: Poor appetite, vomiting after meals, abdominal pains, diarrhea for 4 months. January 23, 1929: 200 cc. oxygen; January 30: 800 cc.; February 13: 600 cc.; February 23: 600 cc.; March 13: 800 cc. Result: Appetite much improved, diarrhea ceased, vomiting after meals not as much as before, some gastric distress persisted. Patient died five weeks after last inflation.

CASE 3.—M. S., aged 30 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes for 3 years. Gastrointestinal symptoms: Nausea, vomiting after meals, constipation alternating with diarrhea began 2 years ago. January 23, 1929: 850 cc. oxygen. Relief from symptoms. Normal stools. Died 3 weeks after treatment.

CASE 4.—P. W., aged 26 years, white, male. Far-advanced pulmonary tuberculosis for 3 years. Gastrointestinal symptoms during last 5 months: Lack of appetite, occasional emesis after meals, cramping pains, constipation alternating with diarrhea. January 26, 1929: 450 cc. oxygen; January 30: 800 cc. Appetite improved, complete relief from other symptoms. Pains returned 6 weeks, and diarrhea 2 months, after treatment. Died 3 months after last inflation.

CASE 5.—S. S., aged 29 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes for 2 years. Gastrointestinal symptoms: Eructation, nausea, vomiting, severe cramping pains; frequent, very loose, watery stools began 3 months ago. February 1, 1929: 800 cc. oxygen; February 8: 800 cc.; February 15: 850 cc.; February 23: 900 cc.; March 13: 1000 cc.; March 22: 1000 cc.; April 5: 1200 cc. Number of stools decreased from 8 to 12 to 3 to 6 in 24 hours. Consistency of stools somewhat improved. Nausea, emesis and abdominal pain persisted in a less severe form. Discharged against advice.

CASE 6.—C. O., aged 24 years, white, male. Far-advanced pulmonary tuberculosis of 8 months' duration. All lobes involved. Lack of appetite, nausea, vomiting, diarrhea for 1 month. February 1, 1929: 700 cc. oxygen. No relief. Died 2 weeks after inflation.

CASE 7.—R. C., aged 44 years, white, male. Far-advanced pulmonary tuberculosis began 5 years ago. All lobes involved. Gastrointestinal symptoms of 9 months' duration: "Indigestion," constipation alternating with diarrhea, diarrhea predominating. February 6, 1929: 700 cc. oxygen; February 20: 800 cc. Diarrhea ceased, stools became formed. Died 2 weeks after last inflation.

CASE 8.—J. M., aged 52 years, white, male. Pulmonary tuberculosis, involving all lobes, began 14 years ago. Intestinal disease with poor appetite, eructation, nausea, vomiting and abdominal pain for 6 months. February 6, 1929: 800 cc. oxygen; February 20: 800 cc.; March 27: 1000 cc.; May 17: 1200 cc. Complete relief from symptoms with the exception of occasional slight recurrences. Discharged with greatly improved general, pulmonary and intestinal condition 5 months after beginning of treatment.

CASE 9.—M. S., aged 21 years, white, female. Far-advanced pulmonary tuberculosis of 2 years' duration. All lobes involved. Intestinal disease with gastric distress, nausea, vomiting after meals, diffuse abdominal pains, constipation and later on diarrhea developed toward the end of second year. February 8, 1929: 800 cc. oxygen; February 26: 800 cc.; March 22: 1000 cc.; April 22: 1000 cc. No symptoms except emesis following first, and slight abdominal pain following last, inflation. Discharged 3 months after start of treatment.

CASE 10.—F. A., aged 46 years, white, male. Pulmonary tuberculosis, involving all lobes, began 13 years ago. Indigestion, abdominal pain, constipation and diarrhea for 8 months. February 12, 1929: 800 cc. oxygen. No improvement. Died 2 months after treatment.

CASE 11.—M. C., aged 37 years, white, male. Far-advanced pulmonary tuberculosis involving both upper and lower lobes, for 6 years. Intestinal disease, with poor appetite, indigestion, nausea, constipation began 11 months ago. February 12, 1929: 500 cc. oxygen. Relief from gastric distress; constipation persisted. Died 16 days after inflation.

CASE 12.—A. B., aged 39 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, for 10 years. Intestinal disease with "indigestion," abdominal pain and constipation during last 7 months. April 9, 1929: 1000 cc. oxygen. No improvement.

CASE 13.—G. D., aged 54 years, white, male. Far-advanced pulmonary tuberculosis of 7 years' duration. Intestinal disease with pyrosis, constipation alternating with diarrhea for 10 months. April 11, 1929: 600 cc. oxygen; April 22: 1200 cc.; May 14: 1400 cc. Pyrosis persisted. Stools normal in frequency and consistency. Died 1 month after last inflation.

CASE 14.—D. B., aged 17 years, white, male. Far-advanced pulmonary tuberculosis of 1 years' duration. Entire left lung and right upper lobe involved. Intestinal disease, with nausea, vomiting after meals, diffuse abdominal pains, diarrhea for 5 months. April 18, 1929: 1000 cc. oxygen; May 9: 1000 cc. No improvement. Died 15 days after last inflation.

CASE 15.—R. N., aged 21 years, white, male. Far-advanced pulmonary tuberculosis began 2 years ago. All lobes involved. Poor appetite and diarrhea for 3 months. April 18, 1929: 1000 cc. oxygen; May 9: 1000 cc.; June 1: 1400 cc.; June 14: 1050 cc.; July 22: 1000 cc. Appetite much better; diarrhea ceased except on the eighth day following second inflation. Appetite became poor after fourth oxygen injection. Diarrhea recurred 9 days after last inflation. Died 2 weeks after last treatment.

CASE 16.—A. K., aged 23 years, white, male. Far-advanced pulmonary tuberculosis involving all lobes for 1 year. Intestinal disease with lack of appetite, gastric distress and diarrhea began 1 month ago. April 30, 1929: 950 cc. oxygen; May 9: 1000 cc.; May 29: 1000 cc.; June 14: 600 cc. No improvement. Died 1 month after last treatment.

CASE 17.—A. L., aged 19 years, white, male. Far-advanced pulmonary tuberculosis of 6 years' duration. "Heart burn," nausea, diffuse abdominal pains and diarrhea for 7 months. May 14, 1929: 1000 cc. oxygen; May 29: 1000 cc.; June 12: 1200 cc.; June 24: 1000 cc.; July 9: 1000 cc.; February 14: 300 cc.; February 21: 600 cc.; March 7: 600 cc. Gastrointestinal symptoms much improved, diarrhea ceased following first five inflations. Complaints gradually reappeared 17 days after treatment was discontinued. No relief was observed by repeated inflations instituted 5 months later. Died 2 weeks after last treatment.

CASE 18.—F. G., aged 19 years, white, male. Far-advanced pulmonary tuberculosis for 1 year. Both upper and lower lobes involved. Gastrointestinal symptoms: Lack of appetite, gastric distress, abdominal pain, cramping in character, diarrhea for 2 months. May 15, 1929: 1000 cc. oxygen; May 29: 1300 cc.; June 12: 1000 cc.; June 24, 1500 cc.; July 9: 1200 cc.; July 23: 1200 cc.; August 13: 1000 cc.; August 31: 1000 cc. No relief. Died 2 weeks after last inflation.

CASE 19.—A. H., aged 39 years, white, female. Far-advanced pulmonary tuberculosis, involving both upper and left lower lobe, for 4 years. Intestinal symptoms began 8 months ago: Nausea, vomiting, severe abdominal pain after meals, diarrhea. June 1, 1929: 600 cc. oxygen. No improvement. Died 2 months after treatment.

CASE 20.—M. H., aged 29 years, white, female. Far-advanced pulmonary tuberculosis for 10 years. All lobes involved. Intestinal disease with poor appetite, gastric pains and diarrhea began 14 months ago. June 1, 1929: 400 cc. oxygen; June 24: 850 cc.; July 9: 1000 cc.; July 23: 1000 cc.; August 13: 1000 cc.; August 27: 1000 cc.; September 11: 1000 cc.; September 30: 1000 cc.; October 14: 1000 cc.; October 28: 950 cc.; November 19: 600 cc.; December 10: 700 cc.; December 21: 500 cc.; January 23, 1930: 500 cc.; February 6: 600 cc.; February 21: 600 cc.; March 15: 500 cc.; March 29: 500 cc.; April 12: 500 cc.; April 26: 500 cc. Complete relief from intestinal symptoms, lasting from 11 to 32 days, when inflation had to be repeated. General and pulmonary condition improved during course of treatment. Inflations were discontinued because of intraäbdominal adhesions causing considerable discomfort in last one-third of treatment.

CASE 21.—K. F., aged 45 years, white, male. Pulmonary tuberculosis began 5 years ago. All lobes involved. Gastrointestinal symptoms: Gastric distress following meals, nausea, vomiting, diffuse abdominal pains, diarrhea for 2 months. July 10, 1929: 1000 cc. oxygen; July 20: 1200 cc. No improvement. Died 2 months after treatment.

CASE 22.—L. R., aged 21 years, white, male. Pulmonary tuberculosis, involving entire left lung, with cavitation, began 3 years ago. Intestinal disease with gastric distress and diarrhea for 3 months. July 12, 1929: 1000 cc. oxygen. No improvement. Discharged against advice.

CASE 23.—C. N., aged 29 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, for 6 months. Indigestion, abdominal pains, cramping in character, diarrhea for 1 month. July 20, 1929: 1000 cc. oxygen. No improvement. Died 3 weeks after inflation.

CASE 24.—M. X., aged 31 years, white, male. Pulmonary tuberculosis, involving all lobes, began 1 year ago. Gastrointestinal symptoms: Gastric distress, diffuse abdominal pain, constipation alternating with diarrhea, diarrhea predominating for five months. July 22, 1929: 1000 cc. oxygen. Number of bowel movements reduced from 5 to 9 to 2 in 24 hours. Consistency of stools about normal. Relieved from abdominal discomfort. This effect lasted for 23 days, when pain and diarrhea recurred. Died 6 weeks after inflation.

CASE 25.—R. M., aged 27 years, white, male. Far-advanced pulmonary tuberculosis, involving both upper and left lower lobes, for 8 months. Intestinal disease with cramping abdominal pains, most marked in the right lower quadrant, and diarrhea began 3 months ago. September 6, 1929: 1000 cc. oxygen; September 25: 1000 cc.; October 10: 1200 cc. Number of bowel movements decreased from 10 to 13 to 4 in 24 hours. No abdominal pains. Patient's general appearance and mental attitude greatly improved. Discharged against advice.

CASE 26.—H. B., aged 21 years, white, female. Far-advanced pulmonary tuberculosis, involving both upper and lower lobes. Duration of pulmonary disease, 2 years. Gastrointestinal symptoms: Indigestion, abdominal pains, nausea, vomiting, constipation alternating with diarrhea, diarrhea predominating for 2 months. September 30, 1929: 300 cc. oxygen; October 9: 750 cc.; October 23: 800 cc.; November 6: 800 cc.; November 22: 900 cc.; December 6: 1000 cc.; January 7, 1930: 1000 cc. Complete relief from gastrointestinal symptoms. Stools normal in frequency and consistency.

CASE 27.—B. P., aged 23 years, white, female. Far-advanced pulmonary tuberculosis involving all lobes for 1 year. Intestional disease with lack of appetite, nausea, vomiting after meals, cramping pains, 12 to 14 watery stools daily. October 7, 1929: 550 cc. oxygen. Free from nausea, vomiting and abdominal pain. Stools though watery in character reduced to 6 to 7 in 24 hours.

CASE 28.—F. S., aged 19 years, white, female. Far-advanced pulmonary tuberculosis of 14 months' duration. All lobes involved. Lack of appetite, gastric pain, emesis after meals, pain in right lower quadrant, diarrhea for two months. October 23, 1929: 700 cc. oxygen. Abdominal pains and gastric distress ceased. Stools of better consistency, though not decreased in number. Died 3 months after treatment.

CASE 29.—J. W., aged 30 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, began about 1.5 years ago. Intestinal disease with anorexia, pyrosis, nausea, vomiting and diarrhea for 2 months. October 26, 1929: 1000 cc. oxygen. All symptoms disappeared. Stools normal in number and consistency.

CASE 30.—B. W., aged 22 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes for 8 months. Gastrointestinal symptoms: Anorexia, distress after eating, abdominal pain and constipation developed six months ago. November 8, 1929: 1000 cc. oxygen; November 22: 700 cc.; November 29: 700 cc.; December 6: 750 cc.; December 13: 600 cc. No relief from abdominal symptoms. Constipation ceased. Patient had 2 to 3 loose stools from first to third inflation. One stool of medium soft consistency from that time on until death. Died 2 months from start of treatment.

CASE 31.—W. K., aged 48 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, began 3 years ago. Intestinal disease with anorexia, abdominal pain, constipation followed by diarrhea for 7 months. December 5, 1929: 1000 cc. oxygen; December 18: 600 cc.; January 7, 1930: 500 cc.; February 1: 500 cc.; February 14: 300 cc.; March 7: 300 cc. Abdominal pain greatly relieved, though occasionally recurred. Stools not as loose as formerly; no change in their number. Died 5 months after beginning of treatment.

CASE 32.—J. P., aged 58 years, white, male. Moderately advanced pulmonary tuberculosis, involving both upper and right middle lobes, for 1 year. Intestinal disease with gastric distress and constipation began 2 months ago. January 8, 1930: 1000 cc. oxygen; January 23: 500 cc. Relieved from gastric distress and constipation. Constipation recurs occasionally since treatment was discontinued 13 months ago. Patient's general and pulmonary condition is stationary.

CASE 33.—J. G., aged 27 years, Indian, male. Far-advanced pulmonary tuberculosis, involving entire right lung, with cavitation, for 1 year. Indigestion, gastric pain after eating, diffuse abdominal pain for six weeks. No diarrhea or constipation. January 8, 1930: 1000 cc. oxygen; January 25: 750 cc.; February 4: 600 cc.; March 7: 650 cc. Complete relief from symptoms. Symptom-free for 11 months.

CASE 34.—M. W., aged 37 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes, began 3 years ago. Intestinal disease with indigestion, nausea, flatulence and constipation for 3 months. January 18, 1930: 1000 cc. oxygen; February 6: 1000 cc.; February 21: 800 cc. Normal stools, rarely recurring gastric distress. General and pulmonary condition improved. Discharged 3 months after last inflation.

CASE 35.—M. S., aged 18 years, white, female. Far-advanced pulmonary tuberculosis of 1 year's duration. All lobes involved. Gastrointestinal symptoms: Lack of appetite, cramping pain and diarrhea for 2 months. January 28, 1930: 1000 cc. oxygen; February 6: 1000 cc.; February 21: 800 cc.; March 7: 800 cc.; March 21: 800 cc.; April 8: 600 cc. No improvement.

CASE 36.—E. B., aged 23 years, white, male. Far-advanced pulmonary tuberculosis, involving entire right lung and left upper lobe, began 1 year ago. Intestinal disease with pyrosis, nausea, vomiting, diffuse abdominal pains, diarrhea for 9 months. May 2, 1930: 1000 cc. oxygen; May 13: 1000 cc.; May 20: 650 cc.; June 3: 650 cc.; July 30: 150 cc. Gastric distress and abdominal pains not relieved. Number of stools decreased from 5 to 6 to 2 in 24 hours. All symptoms recurred shortly after treatment was discontinued, in June. When treatment was resumed, in July, the patient's tolerance was so far diminished that further inflations seemed inadvisable. Patient's general, pulmonary and intestinal condition is getting worse gradually.

CASE 37.—B. S., aged 38 years, white, female. Far-advanced pulmonary tuberculosis of 7 years' duration. All lobes involved. Lack of appetite, nausea and vomiting after eating, indigestion, flatulence, abdominal pains, constipation alternating with diarrhea, constipation predominating. May 2, 1930: 1000 cc. oxygen; June 3: 1000 cc.; July 8: 1000 cc.; July 30: 900 cc.; August 27: 850 cc.; September 16: 1000 cc.; September 29: 1200 cc.; October 18: 1200 cc.; November 1: 1200 cc.; November 15: 1200 cc.; November 25: 1200 cc.; December 9: 1000 cc. Relief from abdominal pains and constipation; diarrhea occasionally recurred. Gastric distress after meals persists.

CASE 38.—G. S., aged 37 years, white, male. Far-advanced pulmonary tuberculosis, involving entire right lung and left upper lobe, for 5 years. Intestinal disease with gastric distress after eating, vomiting, abdominal pains, cramping in character, diarrhea for 3 months. May 3, 1930: 1000 cc. oxygen; May 13: 1000 cc.; May 20: 800 cc.; May 27: 900 cc.; June 3: 800 cc. No relief. Died 3 weeks after last inflation.

CASE 39.—R. B., aged 26 years, white, male. Far-advanced pulmonary tuberculosis, involving both upper and lower lobes, began 2 years ago. Intestinal disease with capricious appetite, pyrosis, diffuse abdominal pains and diarrhea for 5 months. May 3, 1930: 700 cc. oxygen; May 13: 800 cc. Complete relief from abdominal symptoms. Stools normal in frequency and consistency. Died 8 days after last inflation.

CASE 40.—J. S., aged 42 years, white, male. Far-advanced pulmonary tuberculosis of 4 years' duration. Both upper and lower lobes involved. Indigestion, abdominal pain, diarrhea for seven months. August 20, 1930: 1000 cc. oxygen; September 2: 1000 cc. Diarrhea disappeared. Slight abdominal pains recurred occasionally. Died 10 days after last treatment.

CASE 41.—T. P., aged 18 years, white, male. Far-advanced pulmonary tuberculosis, involving entire left lung and right upper lobe, for 1.5 years. Intestinal disease with loss of appetite, nausea, vomiting, cramping pains and diarrhea for 6 months. August 27, 1930: 650 cc. oxygen; September 6: 800 cc.; September 9: 900 cc.; September 13: 700 cc.; September 19: 1000 cc.; September 23: 950 cc. Abdominal distress somewhat relieved. Diarrhea lessened; stools less in number but watery in character. Died 1 week after last inflation.

CASE 42.—D. P., aged 21 years, white, female. Far-advanced pulmonary tuberculosis, involving entire right lung and left upper lobe, for 1 year. Intestinal disease with severe abdominal pains and diarrhea for 2 months. August 8, 1930: 1000 cc. oxygen. Number of stools decreased from 3 to 7 to 2 to 3 in 24 hours. Abdominal pain less pronounced. Diarrhea and cramping pains recurred in 6 weeks after inflation. Died 2 months after treatment.

CASE 43.—W. K., aged 21 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes, began 1 year ago. Intestinal disease with nausea, emesis, diffuse abdominal pain and diarrhea for 1 month. September 16, 1930: 1500 cc. oxygen; September 23, 1200 cc. Free from gastric distress and abdominal pain. Diarrhea ceased. Stools normal in consistency.

CASE 44.—H. O., aged 34 years, white, female. Far-advanced pulmonary tuberculosis of 6 years' duration. All lobes involved. Poor appetite, nausea, vomiting, abdominal pain, constipation alternating with diarrhea for 1 year. September 16, 1930: 700 cc. oxygen. No relief.

TABLE 1.—SYMPTOMATIC RESULTS OF PNEUMOPERITONEUM.

Results.	Number of inflations.										Cases.	Per cent.
	1.	2.	3.	4.	5.	6.	7.	8.	12.	20.		
Complete relief	3	6	..	2	1	..	1	..	..	1	14	31.8
Diarrhea ceased, other symptoms persistent	..	1	2	..	1	..	..	1	..	..	5	11.3
Diarrhea persistent, other symptoms ceased	2	..	..	..	..	..	..	..	..	..	2	4.7
Partial relief from all intestinal symptoms	2	..	1	1	2	2	1	..	1	..	10	22.7
No relief	7	2	..	1	1	1	..	1	..	..	13	29.6

Summary. 1. Forty-four cases of tuberculous enterocolitis treated by pneumoperitoneum are reported.

2. The technique of this procedure is simple and practically without danger.

3. The amount of oxygen and the frequency of the inflations should be adapted to the individual case.

4. The subjective feeling of the patient during operation is a far better indicator than the manometer.

5. The abdomen should rather be underinflated than overinflated.

6. No treatment should be given during the menstrual period.

7. Paradoxical oscillations in the manometer were observed in 3 cases.

8. The abdominal capacity markedly decreased in some cases as the course of treatment progressed.

9. A case of bilateral phrenic nerve block and a case of bilateral artificial pneumothorax simultaneously treated by pneumoperitoneum are cited.

10. The therapeutic effect of this procedure is considered to be due to the direct chemical influence of oxygen, the increased intra-abdominal pressure and the hyperemia of the peritoneum and intestinal serosa.

11. Symptomatic relief was noted in 31 (70.4 per cent) of this group.

12. Complete relief was seen in 14 (31.8 per cent), partial relief from all intestinal symptoms in 10 (22.7 per cent); diarrhea ceased while other symptoms persisted in 5 (11.3 per cent); diarrhea persisted while other symptoms ceased in 2 (4.7 per cent).

13. The duration of symptomatic relief varied from a few days to 2 years.

14. There was no relief in 13, or 29.6 per cent.

15. If it is true that adequate nutrition is the keystone of defense of the body against tuberculosis, the rehabilitation of the subcompetent tuberculous intestines by restoring their normal motility

and digestive function is of prime importance. Our therapeutic efforts should be proportionate to the misery and distress of those suffering with this serious complication. The results of our limited experience are encouraging enough to advocate the more frequent use of pneumoperitoneum in the treatment of intestinal tuberculosis.

REFERENCES.

1. Schwatt, H., and Steinbach, M. M.: Tuberculosis of the Intestines, Am. Rev. Tuberc., 1923, **8**, 1.
2. Walsh, J.: New York Med. J., 1909, **90**, 100.
3. Engelsmann, R.: Beitr. z. klin. d. Tuberk., 1917, **38**, 16.
4. Stewart, D. A.: Theses on Intestinal Tuberculosis, Am. Rev. Tuberc., 1927, **15**, 588.
5. Paterson, R. C.: Intestinal Tuberculosis, Am. Rev. Tuberc., 1920, **4**, 433.
6. Smithies, F., Weisman, M., and Fremmel, F.: Tuberculous Enterocolitis, J. Am. Med. Assn., 1928, **91**, 1952.
7. Brown, L., and Sampson, H. L.: Intestinal Tuberculosis, Philadelphia, Lea & Febiger, 1926.
8. Erickson, R. J.: The Symptoms of Intestinal Tuberculosis, Am. Rev. Tuberc., 1925, **12**, 1.
9. Steinbach, M. M.: Comparative Radiographic and Anatomic Studies of Intestinal Tuberculosis, Am. Rev. Tuberc., 1930, **21**, 77.
10. Kantor, J. L.: The Prevention and Treatment of Digestive Disorders in Tuberculous Patients, Am. Rev. Tuberc., 1924, **9**, 430.
11. Rolleston, H. D.: Diseases of the Small Intestine, Allbutt's System of Medicine, London, Macmillan Company, 1907, **3**, 570.
12. Archibald, E.: Surgical Treatment of Intestinal Tuberculosis, Am. Rev. Tuberc., 1917, **1**, 449.
13. Bacmeister, A.: Die Roentgen Behandlung d. Lungen und Darmtuberkulose, Strahlentherapie, 1921, **12**, 227.
14. Bainbridge, W. S.: The Intraäbdominal Administration of Oxygen, Ann. Surg., 1909, **49**, 305.
15. Burkhart, quoted by Bainbridge.
16. Stein, A.: Oxygen Inflation of the Peritoneal Cavity in Tuberculous Exudative Peritonitis, J. Am. Med. Assn., 1922, **78**, 718.
17. Mattick, W. L.: Intraperitoneal Oxygen Inflation in the Treatment of Ascitic Tuberculous Peritonitis, Am. Rev. Tuberc., 1924, **8**, 473.
18. Gilbert, O. M.: Pneumoperitoneum in the Treatment of Tuberculous Peritonitis, Am. Rev. Tuberc., 1924, **8**, 479.
19. Laney, R. L.: The Pneumoperitoneum Treatment of Tuberculous Enterocolitis, Am. Rev. Tuberc., 1924, **9**, 425.
20. Hayes, E. W.: Oxygen Inflation for Tuberculous Peritonitis, Am. Rev. Tuberc., 1926, **13**, 27.

CHRONIC BASAL NONTUBERCULOUS PULMONARY INFLAMMATION.

Its Etiologic Significance.

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The following investigation was prompted by the concern shown by parents now visiting clinics and private physicians for possible pulmonary tuberculosis occurring among their children. Although this manifestation which I am about to describe occurs far more

frequently in children, adults are not altogether free.[9] Chronic nontuberculous inflammation of the mucosa along the basal bronchi at first may be looked upon as a benign disease having cough as its chief manifestation; and it is cough[9] that excites the parents' forebodings. Fortunately we can tell some that their concern is needless since cough is an infrequent symptom of childhood tuberculosis, especially if the onset is acute. With this, however, they should not be dismissed; we shall see subsequently that very grave anatomic and pathologic changes may exist.

Symptomatology. Many of these patients have no other complaint than cough with expectoration. Acute exacerbations with fever, malaise, hoarseness and an increase in all chest symptoms are common; and it is observed by the parents of the patients as well as by older individuals afflicted with the same disease that these acute attacks are much more frequent than acute colds suffered by their associates. They last 2 days to 1 week and fade into the chronic stage again, with occasional persistent cough and expectoration between attacks. Growth, weight, feeling of well-being and general appearance of the patient do not suffer any interference.[9] Ochsner and Nesbit[13] described a mild neurosis accompanying this condition later in life when bronchiectasis developed.

Physical Examination. During the chronic stage there are only a few physical signs indicative of this disease. A mild pharyngitis is common; tonsillitis and facial sinusitis is no more common than in normal individuals, and when present is likely to be a response to secondary infection from the basal bronchi; thoracic contour is not altered; breathing may be a little more frequent and deeper than normal; there is seldom clubbing of the nails. A mild impairment of the percussion note over the bases may exist. Tactile fremitus, vocal resonance and expansion are not disturbed, but the breathing may be harsh. Crepitant râles are usually present,[3] and these are increased in number when elicited in the manner of pertussis râles. During the acute stages râles are always present; between attacks, contrary to Stewart's[3] observation, they may disappear completely. These râles are located over the bases posteriorly or laterally.[3] When they are found throughout the chest a generalized bronchitis exists. Waldbott[16] described an allergic bronchitis that is confused with other forms of pulmonary disease.

Laboratory Examinations. The sputum is densely purulent during the acute stages and may become seropurulent during remissions. Pus cells and the various organisms found along the respiratory tract are present when microscopic examination is made. No one organism seems to predominate; spirochetes and fusiform bacilli are uncommon and seem to have no significance. Charcot-Leyden crystals and Curschmann's spirals are not present.

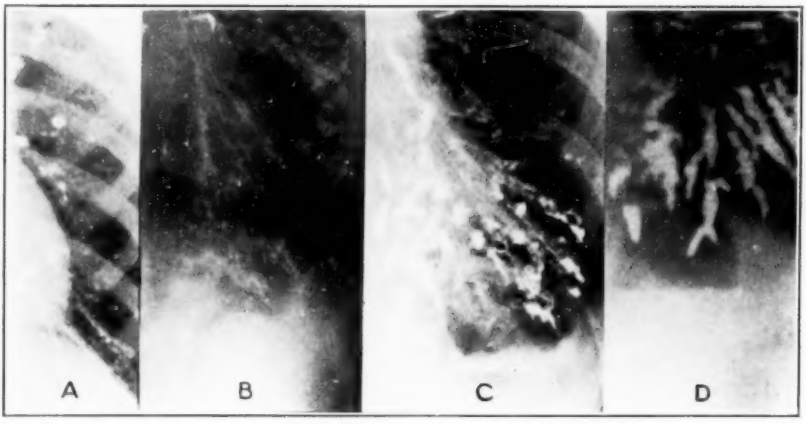

FIG. 1. —*A*, Left bronchi slightly widened; symptoms characteristic. A boy aged 10 years. *B*, At first signs of lung abscess of the left base; rapid improvement, with disappearance of expectoration and râles. Widening confined entirely to the left base. Girl aged 13 years. *C*, Free of cough; postural drainage did not produce sputum. Widening confined to left base. Girl aged 18 years. *D*, Male, 30 years, having all the symptoms of frank bronchiectasis. Probably a congenital widening and permanently infected, with irradicable cough. Lung abscess is the brigand in the dark awaiting them.

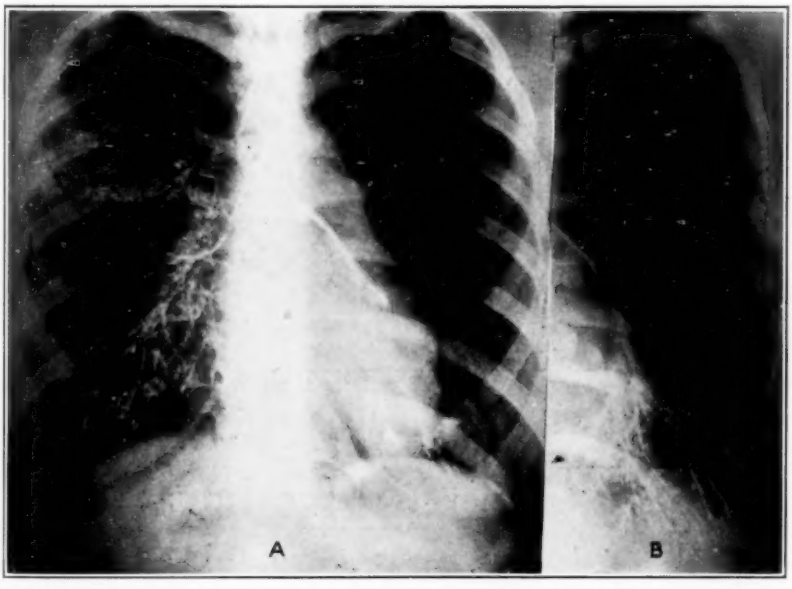

FIG. 2. —*A*. Roentgenogram showing normal bronchi on the right side and slight widening of the bronchi on the left. This patient had all the signs of chronic basal inflammation due to widening. She was twenty-five years of age and had been troubled with attacks of productive cough since childhood. Subsequent lipiodol introduction revealed the bronchi extending into the costophrenic angle on the left side to have reached a pathologic change. *B*. An asthmatic bronchus.

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Roentgenologic Examination. Single or stereoscopic films without lipiodol injection may show nothing. If the patient has not coughed and expectorated for several hours before[8] films are taken or if the patient is having an acute reactivation at the time, there may be indistinct areas of increased opacity along the basal trunks. Miller and Eglee[8] are of the same opinion, while Hebert[6] found increased translucency due to emphysema. Since the introduction of lipiodol by Sicard and Forestier[18] much of the uncertainty associated with pulmonary skiagraphy has been overcome and in no instance has itsdiff erential benefits been more revolutionizing than in basal pulmonary inflammation. Until now the syndrome has been treated as a single entity. Early in the life of the patient, and from a physical and symptomatic standpoint, no other course could have been possible; but as a result of frequently resorting to bronchography, I have been able to prove conclusively that 62 per cent (Fig. 1) of this series have underlying anatomic changes—bronchial widening—responsible for this clinical syndrome; I have been able to record various stages of widening at different ages so that it would seem beyond doubt that anomalous development is the initiating factor in these cases. The other 38 per cent were found not to have widening, and it is my opinion that these cases never progress into widening and "clinical bronchiectasis" as do the former. In fact, they seem to have the asthmatic type of of bronchus. (Fig. 2, B.) Thus we have two groups: the former, a grave change; the latter, a benign state of lesser importance. So distinctly are the two divided that the following classification is proposed:

Chronic basal nontuberculous pulmonary inflammation.

(*a*) With bronchial widening.

(*b*) Without bronchial widening.

It was observed by Ochsner,[15] Sauerbruch,[2] Grawitz[1] and Duken[10] that widening of the bronchi most frequently occurred on the left. Duken thought[10] that the left pulmonary artery constricted the left main bronchus before the superior branch came off and that the lower branch most commonly came off at an acute angle, all of which would tend to facilitate dilatation. To these suggestions I would like to add the possible influence of a continuously stimulated vagus nerve. The left vagus passes anterior and lateral on the aortic arch, where it may be pounded upon by this pulsating structure, thus stimulating it to dilate the bronchi of its distribution which prolonged would facilitate their abnormal development. This series which was composed almost entirely of children consisted of 50 per cent unilateral left-sided dilatation. That abnormal widening of the basal bronchi has a congenital origin seems undisputable. Grawitz,[1] Sauerbruch,[2] Duken,[10] Meyer[7] and Henschen[7] were of this opinion. Dunham[17] demonstrated malformation of the

entire left bronchial tree. When injected with lipiodol the bronchi were found to simulate the budding of the embryologic stage.

Immediately it is suggested that these cases with widening go on to develop clinical bronchiectasis which they do.[3,8,15] This change is slow in some instances and rapid in others, depending possibly on the frequency of reinfection, daily hygienic surroundings, occupation and the supervening of pertussis, measles or influenza. One of this series was well until the age of 8 years, when he developed pertussis and failed to recover from the cough; Steidel's[14] case gave no symptoms until the age of 25 years, at which time he became infected and had hemoptysis; Villaret's[11] case was free of symptoms until the age of 32 years; another of this series (Fig. 1, C) at the age of 18 years had only periodic attacks of productive cough. During remissions she has been entirely free of cough and expectoration. These cases are strongly confirmative of Bezancon's[12] description of dry bronchiectasis. Ochsner,[9,15] Miller[8] and Eglee[8] were of the opinion that abnormal widening of the bronchi disposed to basal bronchitis and bronchiectasis. These men have worked chiefly on adults. Stoney[5] thought pyorrhea alveolaris frequently was associated with chronic basal bronchitis; Graves, Foster and Hett[4] considered humid and unhygienic surroundings as the most common cause of chronic bronchitis. We find that there are several factors tending to produce chronic basal bronchitis, but the important thing to remember is that bronchial widening is a frequent cause, and when present the prognosis is greatly altered.

Differentiation of the Two Types. Frequent reference has been made to describers of chronic basal bronchitis who believe that congenital widening of the bronchi is an etiologic factor and predisposes to bronchiectasis. The symptomatology of the syndrome has been described; but an investigation for differential purposes and a study of these cases of bronchial widening prior to development of clinical bronchiectasis has been but little studied. I maintain that an early differentiation of the two should be made, for the treatment and prognosis is entirely different.

The only reliable way to differentiate the two is by means of bronchography. Should Roentgen facilities be inaccessible the following are good differential points: If widening exists the cough is apt to be more productive, more chronic; the sputum will be more purulent, and when the patient is put in a position for draining the basal bronchi and told to cough, considerable brownish-yellow or greenish sputum may be produced. This is during attacks; between attacks the sputum may disappear completely. These signs are not entirely reliable.

Conclusions.—1. Basal pulmonary inflammation as described above is nontuberculous.

2. These cases can be grouped as follows: (*a*) With bronchial widening; (*b*) without bronchial widening.

3. When widening exists it is much more common on the left; there are strong indications that anomalous development is the cause, and the prognosis is grave.

4. When widening is absent the chances for recovery are assured.

5. There is no specific organism responsible.

SUMMARY OF CASES.

	Negative.	Positive.		
Mantoux test	4*	19		
Family history of pulmonary tuberculosis	19	4		
Upper respiratory infection	14	9		
		L.	R.	R.&L.
Congenital widening	9	12	0	2
Average age	13.5 yrs.	(Oldest 33 yrs. and youngest, 6 yrs.)		

* Figure is number of cases. Total number of cases was 23.

BIBLIOGRAPHY.

1. Grawitz: Virchow's Arch. f. path. Anat., 1888, **82**, 217.

2. Sauerbruch, E.: Proc. Third Cong. Internat. Soc. Surg., Brussels, 1911, p. 269.

3. Stewart, C. A.: Chronic Nontuberculous Basal Pulmonary Diseases in Childhood, a chapter in Tuberculosis Among Children, by J. Arthur Myers, Springfield, Ill., Charles C. Thomas, Publisher.

4. Graves, Foster and Hett: Climatic Treatment of Chronic Bronchitis, British Med. J., 1923, **2**, 1140.

5. Stoney, F.: General discussion of paper by Greves, Foster and Hett: Ibid., p. 143.

6. Hebert, G. T.: Basal Fibrosis in Children, Lancet, 1922, **1**, 1145.

7. Meyer, W., and Henschen, C.: Results and Prospects of Surgical Treatment of Tuberculosis of the Lungs and of Bronchiectasis, Trans. Am. Surg. Assn., 1914, **32**, 547.

8. Miller, J. A., and Eglee, E. P.: Bronchograms in the Study of Pulmonary Disease, Am. Rev. Tuberc., 1927, **16**, 19.

9. Ochsner, A.: Unappreciated Causes of Chronic Bronchitis, J. Am. Med. Assn., 1929, **93**, 188.

10. Duken, J. P.: Klinische und experimentelle Studien zur Pathogenese und Diagnostik der Bronchiektasie im Kindersalter, Ztschr. f. Kinderheilk., 1927, **44**, 1.

11. Villaret, M., Dumont, J., and Saint Girons, F.: Congenital Bronchiectasis in Adults, Paris méd., 1925, **1**, 150.

12. Bezancon, F.: Hemoptysis and Dilatation of Bronchi, Presse méd., 1924, **32**, 157.

13. Ochsner, A., and Nesbit, W.: Bronchography: Introduction of Iodized Oil into Tracheobronchial Tree by "Passive" Method, AM. J. MED. SCI., 1928, **175**, 175.

14. Steidel, J.: Personal permit to mention a case of dry bronchiectasis that came under his observation at Trudeau Sanatorium, Trudeau, N. Y.

15. Ochsner, A.: Bronchiectasis, AM. J. MED. SCI., 1930, **179**, 388.

16. Waldbott, G. L.: Allergic Bronchitis, J. Lab. and Clin. Med., 1928, **13**, 943.

17. Dunham, K.: Hamilton County Tuberculosis Sanatorium, Cincinnati, O. (special permit).

18. Sicard, J. A., and Forestier, J.: Iodized Oil as Contrast Medium in Radioscopy, Bull. et mém. Soc. méd. d. hôp. de Paris, 1922, **46**, 463.

TUBERCULOSIS SIMULATING ACUTE LEUKEMIA.

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As a definite relationship between tuberculosis and leukemia has never been established, we present 2 cases to illustrate that a tuberculous infection may produce a clinical picture simulating an acute myeloid leukemia.

Since 1924, 86 cases diagnosed as leukemia have been studied at the Long Island College Hospital and 11 of these showed the presence of pulmonary tuberculosis with leukemoid blood pictures. Nine of these cases are not included in this report because of the absence of postmortem examination.

Patients suffering from chronic leukemia may die of pulmonary tuberculosis and occasionally pulmonary tuberculosis may give rise to a qualitative or a quantitative increase in lymphatic cells. Joachim[1] reported a case illustrating that leukemia may give rise to infiltrations of the lung simulating tuberculosis.

The bizarre blood reactions seen in agranulocytosis, in acute mononucleosis and in certain cases of severe infections of non-leukemic origin, are proof that too much reliance cannot be placed upon the blood picture alone.

The difficulties encountered in the final interpretation of these cases are:

1. Did the patients have myeloid leukemia with tuberculosis as a complication?

2. Did they have tuberculosis which so affected the hemopoietic system as to give rise to a leukemic blood picture?

As far back as 1896, Volpe[2] discussed the association of tuberculosis and leukemia and in 1902 Quincke published a case report illustrating this association. Many observers stress the frequent occurrence of tuberculosis with leukemia and in 1913 Nanta[4] collected 37 cases of myeloid leukemia and tuberculosis.

The consensus of opinion is that tuberculosis is superimposed upon the leukemia and the tuberculosis becomes active after the body resistance has been lost because of leukemia.[6,7,8]

Mönckeberg[3] suggests that tuberculosis may so alter the leukemic

reaction that at autopsy one may not find anything characteristic of the leukemia.

Case Reports.—Case 1. G. S., a white female, aged 30 years, entered the Long Island College Hospital complaining of vaginal bleeding and weakness for 3 months. At the regular menses the flow lasted 10 to 15 days instead of the usual 4 to 5. Between periods spotting was present and at autopsy this bleeding was found to be due to an eroded pedunculated fibroid. The weakness, gradual in onset and described as an early fatigue, had become so severe that the patient was confined to bed. The family history as well as the past personal history disclosed nothing of note.

Physical Examination. A young, adult female showing good nutrition but a definite pallor. Temperature, 101.2° F.; pulse, 100; respiration, 20; blood pressure, 100 systolic and 60 diastolic. Fifteen to 20 small, discrete lymph nodes, 1.5 cm. in size, were present at either side of the neck. Harsh bronchovesicular breath sounds with small bubbling râles on deep inspiration were heard at both upper lung lobes. Neither liver nor spleen was palpable. The vaginal bleeding was present.

Laboratory Findings. The Wassermann reaction was negative. The urine showed a specific gravity of 1020, no albumin, no sugar. Microscopic examination of a catheterized specimen was negative. Blood chemistry: sugar, 110 mgm.; urea, 28.1 mgm.; uric acid, 3.4 mgm.; creatinin, 1.3 mgm. Blood culture was sterile. Throat culture showed a hemolytic streptococcus. Sputum examination was negative for tubercle bacilli. Roentgen ray of chest revealed "tuberculous changes" scattered throughout both lungs.

Clinical Course. Weakness and restlessness were the outstanding symptoms. The vaginal bleeding responded only temporarily to blood transfusions. Temperature was intermittent, varying between 101° and 105°. There was marked respiratory difficulty and extreme exhaustion upon the slightest exertion. Pulse was 120 to 160 and respirations were 20 to 40. Air hunger and stupor were the outstanding terminal symptoms.

Table 1.—Blood Findings of Case 1.

Date.	R. B. C. per c.mm., in millions.	W. B. C. per c.mm., in thousands.	Hgb., per cent.	Platelets per c.mm.	Ret., per cent.	N.P., per cent.	S.M., per cent.	My. O.P., per cent.	My. O.N., per cent.	N. My., per cent.	U.C., per cent.	Bl. T., minutes.
November 10	2.4	7.0	50	130,000	1	2	6	20	53	13	6	8
*November 13	2.9	5.2	54	....	..	9	..	58	23	10	10	
*November 20	..	5.7	62	....	..	5	..	52	20	13	10	
November 25	..	7.4	68	....	..	3	..	80	12	5	5	
December 1	2.2	24.0	..	....	..	2	..	74	5	19	0	
December 6	..	2.8	42	....	..	3	..	72	12	13	0	

Ret. = reticulocytes. N.P. = neutrophilic polymorphonuclears. S.M. = small mononuclears. My. O.P. = myeloblasts oxidase positive. My. O.N. = myeloblasts oxidase negative. N. My. = neutrophilic myelocytes. U.C. = unidentified cells. Bl. T. = bleeding time.

* Confirmed by Dr. Florence Sabin.

Autopsy. All of the organs showed marked anemia. The outstanding pathologic findings were confined to the lungs.

Both *lungs* were considerably smaller than normal and extremely irregular in outline, due to alternately areas of fibrosis and emphysema. Both apices contained old scars. Throughout both upper lobes, the upper portions of both lower lobes and the entire right middle lobe was a fine fibrosis producing a coarsely alveolar structure. Along the lower margin of these areas was a clearly demarcated line of advance of the sclerosing process, apparently fibroid phthiasis. Near the base of the right lower lobe was a calcified nodule which was probably the primary focus. An area of hemorrhagic bronchopneumonia in the right lower lobe was covered by a thin layer of fibrinous pleurisy.

Microscopically, the extensive fibrosis was found to be due to a sclerosing tuberculosis. At the margin of the process were well-formed tubercles containing giant cells. Tubercle bacilli were found in these areas. Surrounding the tubercles and in areas adjacent to the tuberculous foci there was a mononuclear reaction, the cells consisting of lymphocytes and myelocytic cells. In the bronchopneumonic area, the exudate in the alveoli consisted of fibrin, red cells, and mononuclear cells but showed a complete absence of polymorphonuclears.

The *spleen* weighed 190 gm. and showed the gross picture of acute splenic tumor. *Microscopically*, the Malpighian corpuscles were small and densely packed with lymphocytes. The pulp was congested and scattered throughout were lymphocytes and myelocytic cells in about equal numbers. Most of the latter showed a nongranular cytoplasm and appeared to be myeloblasts. A few were definitely granular and were interpreted as myelocytes. Scattered megakarocytes were also found.

The *liver* weighed 1900 gm. Its normal markings were well retained. There was a slight increase in its fat content and a moderate degree of congestion. *Microscopically*, the sections showed cloudy swelling, slight fatty infiltration and congestion. There was only a mild cellular infiltration, consisting of normal lymphocytes, in the portal canals and among the liver cords.

The mesenteric and retroperitoneal *lymph nodes* were somewhat prominent. *Microscopically*, they showed moderate congestion and edema. They contained a good many myelocytic cells but in smaller numbers than in the spleen.

The *kidneys* showed only slight passive congestion and cloudy swelling of the convoluted tubules.

In the cavity of the *uterus* a large pedunculated polyp was found. Its surface was eroded and intensely hemorrhagic.

The *ribs* contained red marrow. The predominant cells were myeloblasts. Very few myelocytes and no polymorphonuclear leukocytes were present.

The *tibia* contained yellow marrow.

The other organs showed no gross or microscopic pathology of note. There was no leukemic infiltration beneath any of the serous surfaces.

Case 2.—An adult male, aged 30 years, entered the Long Island College Hospital complaining of fever (100° to 103° F. for 2 weeks), cough, and weakness. The cough had been present for 3 weeks and was accompanied by blood-streaked expectoration. The weakness was such that the patient was unable to walk. The family history as well as the past personal history was negative.

Physical Examination. An adult male, acutely ill and unable to give a detailed history. Temperature, 103.2° F.; pulse, 120; respiration, 26; blood pressure, 80 systolic and 40 diastolic. Nutrition was poor, skin was moist. The mucous membranes were very pale. The posterior cervical group of lymph nodes were enlarged, partly coalesced and tender. Six to 8 1- to 2-cm. sized nodes were present in either groin. The lungs showed diffuse harsh bronchovesicular breathing with many sibilant and sonorous râles throughout the entire thorax. Dullness was present at the right upper lobe. The spleen was felt at the level of the umbilicus. The liver was not palpable.

Laboratory Findings. The Wassermann test was negative. The urine showed a trace of albumin, no sugar, and 3 to 6 white blood cells per low-power field. Blood chemistry: sugar, 105 gm.; urea, 22.9 mgm.; uric acid, 2.8 mgm.; creatinin, 1.25 mgm. Blood culture was sterile. Sputum was found to contain a pneumococcus type 4 and a streptococcus hemolyticus; no tubercle bacilli were found in 8 consecutive sputum examinations. Roentgen ray of chest was interpreted as pneumonia, right upper lobe, very probably tuberculous.

Clinical Course. The temperature was continued in type for 10 days; the remainder of the time it was intermittent, varying from 100.8° to 103.4° F. The spleen remained enlarged. The lung findings were those of a bronchopneumonia. The patient expired 3 weeks after admission.

TABLE 2.—BLOOD FINDINGS IN CASE 2.

Date	R.B.C. per c.mm., in millions	W.B.C. per c.mm., in thousands	Hgb., per cent.	Platelets per c.mm.	N.P., per cent.	S.M., per cent.	L.M., per cent.	My., per cent.	N. My., per cent.	Eo. My., per cent.	U.C., per cent.
June 18	2.84	57	38	160,000	39	4	2	15	35	3	2
June 22	....	68	34	....	21	3	5	12	30	4	5
June 25	2.56	65	30	....	23	2	6	9	52	3	5
July 2	....	26	50	150,000	36	3	1	5	50	5	0
July 10	2.13	7	40	....	18	2	2	9	65	4	0

N.P. = neutrophilic polymorphonuclears. S.M. = small mononuclears. L.M. = large mononuclears. My. = myeloblasts. N. My. = neutrophilic myelocytes. Eo. My. = eosinophilic myelocytes. U.C. = unidentified cells.

Autopsy. The only striking external feature was a marked fullness of the right thorax.

The right upper and middle lobes of the *lung* were firmly consolidated and their pleural surfaces covered with a thin layer of fibrin. The consolidation was due to a tuberculous pneumonia. Large irregular areas of caseous pneumonia were separated by areas of gelatinous pneumonia. Scattered throughout the right lower lobe and the entire left lung were small caseous nodules ranging from 1 to 5 mm. in diameter. Near the anterior margin of the middle lobe was a small depression beneath which was a calcified nodule, the primary focus. The hilar and mediastinal lymph nodes were greatly enlarged and almost entirely caseous. The lower half of the trachea and both main bronchi were diffusely ulcerated.

Microscopic examination confirmed the above gross findings. A conspicuous feature was the almost complete absence of productive changes. The tuberculous areas were completely necrotic with little or no epithelioid reaction and no lymphocytic or fibroblastic zones. Tubercle bacilli were present in enormous numbers.

The *heart* was small and flabby. The valves and great vessels were grossly normal.

The *spleen* was greatly enlarged and weighed 1170 gm. The normal configuration was in general retained. It was very firm in consistency with moderately thickened capsule through which could be seen scattered irregular areas of necrosis. The surface on cut section showed innumerable miliary tubercules and irregular shaped areas of infarction.

Microscopically there was a moderate degree of fibrosis throughout. The Malpighian corpuscles were almost entirely missing and those remaining were very small and indistinct. The miliary tubercles noted in the gross, consisted of areas of caseation necrosis with narrow epithelioid margins. No peripheral lymphoid or fibrotic zones surrounded these areas and they contained very few giant cells. The pulp was moderately congested and contained many megakaryocytes, large numbers of lymphocytes, myeloblasts, and smaller numbers of myelocytes, erythroblasts and polymorphonuclears. The cells appeared in varying proportions in different areas.

The retroperitoneal and mesenteric *lymph nodes* were moderately enlarged. *Microscopically* they contained myelocytic cells but in much smaller numbers than in the spleen.

The *marrow from the ribs* was very fibrotic. Focal cellular areas contained lymphocytes, myeloblasts and myelocytes in varying proportions. A good many megakaryocytes were also found.

The *liver* was normal in size and shape but heavily studded with miliary tubercles. Surface and cut section otherwise showed no gross pathology. Unfortunately no microscopic study of the liver was made.

The *kidneys* were grossly normal except for cloudy swelling. No tubercles were grossly visible. *Microscopically* there was found a slight passive congestion and cloudy swelling of the convoluted tubules. No tubercles appeared in the section studied. There was no cellular infiltration in any of the renal tissues.

The *gastrointestinal* tract showed no lesions of note. No tuberculous ulcers were found in the ileum, cecum or colon.

The remaining viscera were grossly normal. No gross leukemic infiltration was found beneath any of the serous surfaces.

Discussion. The modern conception of the hemopoietic tissues as a system, together with the newer methods of study of this system, lead us to believe that these tissues may occasionally respond to any infection in such a way as to produce a leukemic blood picture.[9] Some infections give rise to leukopenia, others to leukocytosis, and still others to an agranulocytosis. No one specific organism alone is responsible for such individual reactions.

One is very seldom justified in making a diagnosis from the blood picture alone. Not only must the history and the physical findings of the patient be correlated with the blood picture, but often a

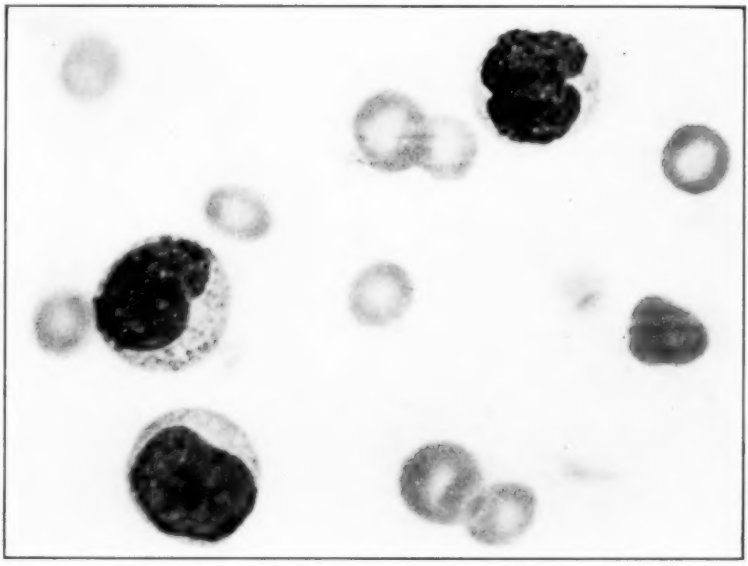

FIG. 1.—Case 1. A field showing three myeloblasts. Wright stain. × 1100.

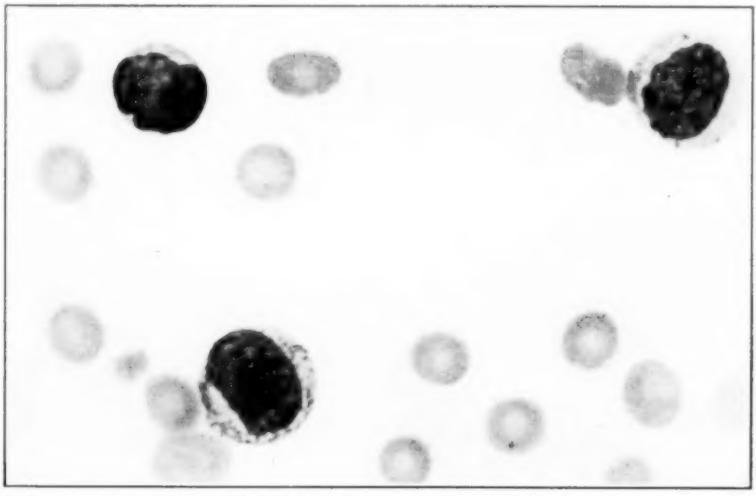

FIG. 2.—Case 1. A field showing three myeloblasts. Oxidase stain. × 1100.

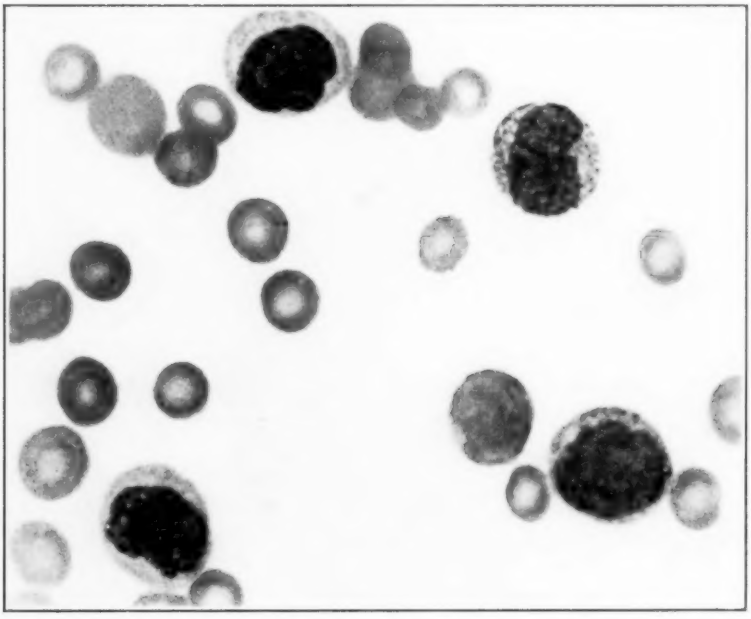

FIG. 3.—Case 2. A field showing three myeloblasts and one metamyelocyte. Wright stain. × 1100.

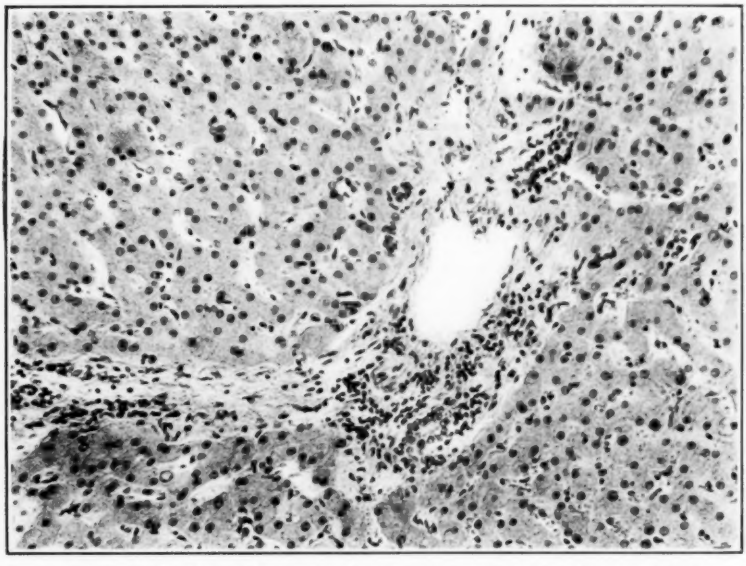

FIG. 4.—Case 1. Section of liver showing absence of typical leukemic infiltrations. × 300.

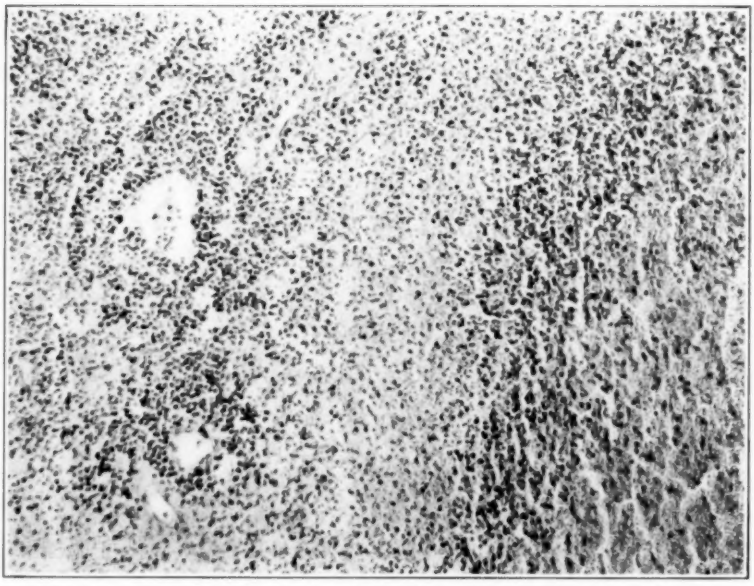

FIG. 5.—Case 2. Section of hilar lymph node showing an area of caseation necrosis surrounded by an ill-defined epithelial zone. × 100.

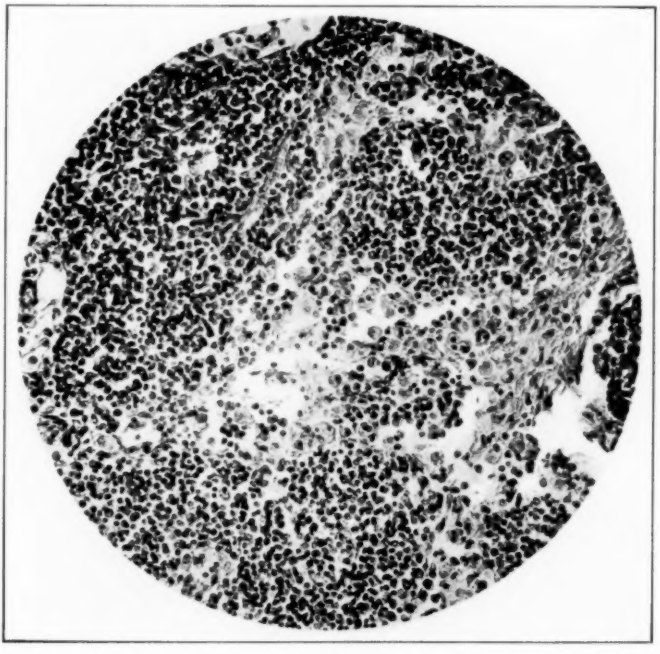

FIG. 6.—Case 2. Section of a nontuberculous lymph node showing large numbers of myelocytic cells and an occasional megakaryocyte. × 300.

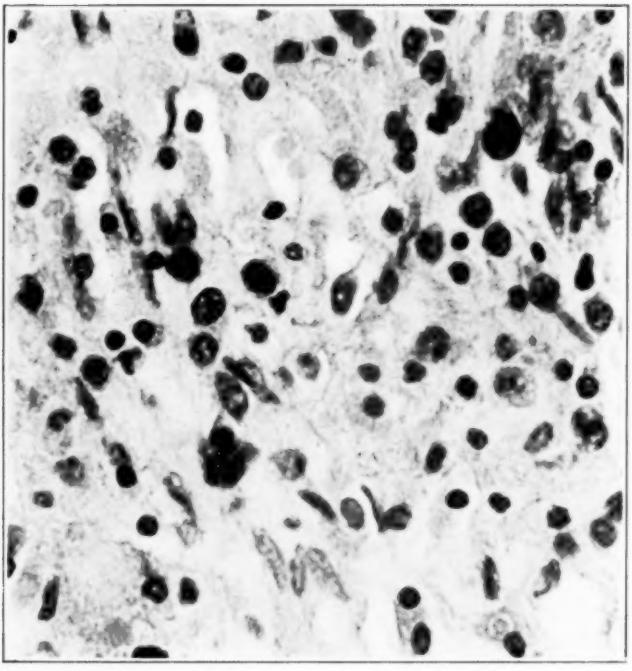

FIG. 7.—Case 2. Section of rib marrow showing diffuse fibrosis, moderate numbers of myeloid cells, several megakaryocytes and an occasional nucleated red blood cell. × 500.

study of the patient's clinical course and final outcome are necessary for the proper final interpretation of that particular case.

In the above reported cases the presence of tuberculosis was the outstanding feature of the postmortem findings. There was absence of characteristic leukemic infiltrations in the tissues, and the spleen, and bone marrow showed only a moderate myeloid hyperplasia, such as one might find in various nonleukemic conditions. Tubercle bacilli were demonstrated in the tissues.

Clinically both patients presented an acute illness of a short duration and therefore the presence of either chronic tuberculosis or chronic myeloid leukemia seemed unlikely. If they had been available for study over longer periods, a more conclusive opinion could have been reached on this point. The severity of the condition associated with a profound anemia and a myeloid blood picture might have justified a clinical diagnosis of acute myeloid leukemia. However, the usual hemorrhagic manifestations were absent. There were neither purpuric spots nor mucous membrane hemorrhages. In the first case there was neither hepatic nor splenic enlargement. In both cases there existed physical signs of pulmonary tuberculosis.

Conclusions. 1. Tuberculosis may so affect the hemopoietic tissues as to give rise to a myeloid leukemic blood picture.

2. We present 2 cases of tuberculous infection, 1 pulmonary, the other generalized, with a myeloleukemoid blood picture and a clinical course simulating acute myeloid leukemia.

NOTE.—The authors wish to express their thanks and appreciation to Dr. Florence Sabin for her aid in identifying the blood cells in Case 1, to Dr. E. B. Krumbhaar and to Dr. L. F. Warren for their coöperation in the interpretation of the above reported cases.

REFERENCES.

1. Joachim, H., and Loewe, L.: Atypical Acute Myeloid Leukemia with Unusual Pulmonary Manifestations, AM. J. MED. SCI., 1927, **174**, 215.

2. Volpe, A.: Arch. int. med., et Clin. Napoli, 1896, **12**, 161.

3. Mönckeberg, B.: Zur Komplikation myeloider Leukämie mit Tuberculosis, Verhandl. d. path. Ges., 1912, **15**, 46.

4. Nanta, A.: Arch. d. mal. du cœur, 1913, **6**, 37.

5. Weil and Coste: Leukemie et Tuberculosis, Bull. et mém. d hôp. de Paris, 1921, **45**, 1019.

6. Wiechman, E.: Miliärtuberkulose und secundäre Myeloblastose, Med. klin., Berlin, 1922, **18**, 102.

7. Piassavy, Bernard and Salmon: Acute Leukemia and Tuberculosis, Bull. et mém. d. hôp. de Paris, 1923, **47**, 1066.

8. Quentin, L.: Case of Atypical Leukemia and Its Relation to Tuberculosis, Bull. et mém. d. hôp. de Paris, 1924, **48**, 31.

9. Krumbhaar, E. B.: Leukemoid Blood Pictures in Various Clinical Conditions, AM. J. MED. SCI., 1926, **172**, 519.

CARBOHYDRATE METABOLISM IN RELATION TO POST-OPERATIVE CRISES IN HYPERTHYROIDISM.*

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The vagaries of the thyroid gland present many matters that deserve thoughtful consideration, and there are many problems relating to the toxic goiter still unsolved. There is general agreement as to the propriety of surgical treatment in the majority of cases; there is no disagreement as to the essentials of the operative program. There are today, it seems to me, two problems of transcending importance, one which has to do with the arrest of the hyperplastic process once it is recognized; the other, with the elimination of operative hazards. In Lugol's solution we have a therapeutic measure which acts like a specific but only for a limited time. What must we add to or substitute for Lugol's solution to render the results permanent? With the exception of the hazards of operation that have to do with the cardiac mechanism, the greatest and most disturbing to me has been the postoperative crisis. Two-thirds of our fatalities are attributed to this, and once a serious crisis is established our efforts to control it have been almost futile. I propose to take for my theme today carbohydrate metabolism and postoperative crises.

The last two decades have added greatly to our knowledge of the physiology of the glands of internal secretion, but there remains still much which we must know before a definite conception of the interrelationship of these structures can be formulated. Within recent years physiologists have attempted to demonstrate the close relationship between the various structures which pour their secretory products into the blood stream, but until we understand more clearly the exact function of each gland and motivating force or forces which bring it into play with other glands, our knowledge of coöperative effect and correlation must be limited. Cannon, more than any other American physiologist, has contributed to this subject. He has suggested the interrelationship between the thyroid and the adrenals, and he has presented evidence which must become more and more important.

For some years I have been much interested in the varying postoperative reactions of the hyperthyroid patient. Why is it that there are such extraordinary variations in the reactions following operation? To be sure we are reasonably certain that the

* An address before the American Association for the Study of Goiter, Kansas City, Missouri, April 9, 1931.

more serious reactions are associated with the highest degree of toxicity. But one can never foretell or forecast a crisis that may threaten the patient's life. It has been said that such reactions may be due to an excess of thyroxin thrown into the circulating blood as a result of the operation, but you well remember crises in the days before the administration of Lugol's solution, when only the superior thyroid vessels may have been ligated and the amount of trauma to the glands negligible.

Four years ago, following the isolation of histamin and cholin from certain structures by Best and others,[1] we utilized a similar technique for their extraction from various types of thyroids. In these we were unable to demonstrate the presence of either of these vasodepressor substances in greater amount per gram of gland in the thyroid adenoma or hyperplastic goiter than that found in the simple colloid goiter. The experiments were clear cut and left no doubt in our minds that these substances could in any way be responsible for the varying reaction observed after operation on the patient for thyroid disease.

However, certain suggestive leads have been published from time to time which may not be amiss to mention here. Schliephake[2] has found that after thyroidectomy dogs are more sensitive to acetylcholin and less sensitive to adrenalin, as measured by their effects on the blood pressure and on the electrocardiogram. When, however, the animals were fed thyroid extract their normal sensitivity to these drugs was restored. It is, therefore, possible that a similar amount of cholin may produce more definite effects in thyroidectomized patients.

Of considerably more interest to me has been a study of the carbohydrate metabolism during the hyperthyroid state. The relationship which thyroid secretion has to the liver and adrenals and possibly also to the pancreas has attracted the attention of many investigators. Cannon and Britton have on a number of occasions referred to the effect of emotional states on the production of glycosuria and hyperglycemia, and Bowman and Kasanin[3] have reviewed this subject thoroughly both from its physiologic and clinical aspects.

Holst,[4] who has made many contributions to the subject of thyroid dysfunction, published, in 1921, the autopsy studies in 4 cases of exophthalmic goiter associated with glycosuria. In these he found a decrease in the islands of Langerhans. Numerous investigators have recognized the fact that experimental diabetes produced by partial extirpation of the pancreas is to an extent controlled by thyroidectomy. Falta[5] found that thyroidectomy is followed by hypertrophy of the islands of Langerhans. Although, in the many observations which appear in the literature there seems to be some conflict, yet the weight of the evidence seems to be that pancreatic and thyroid function affect each other closely. In

support of this contention, certain authors have described a hyperglycemia after operations for hyperthyroidism, but this evidence is not conclusive, since hyperglycemia may occur after any operation where general anesthesia has been used.

Rosenberg[6] carefully studied the glucose-tolerance curves in patients with exophthalmic goiter. He believed that sugar excretion was increased in this disease, but the tolerance curves do not parallel the severity of the clinical symptoms. With both of these deductions John[7] agrees, in that he has obtained similar curves after glucose-tolerance studies, and he states that his findings suggest "an increased permeability of the renal filter during active hyperthyroidism."

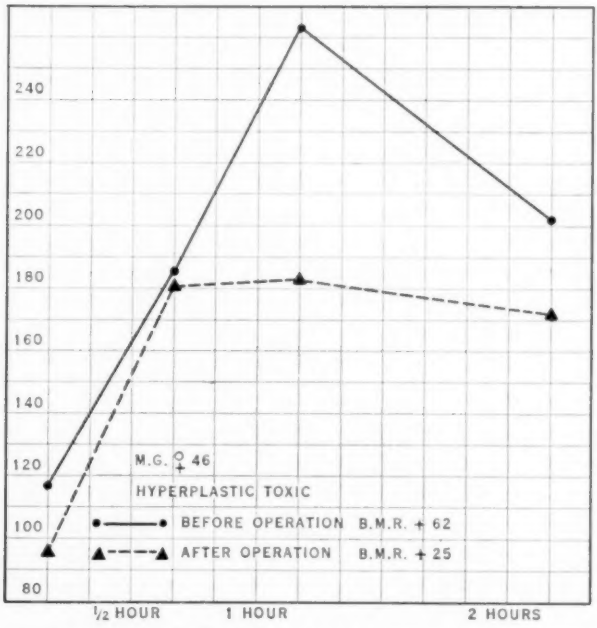

CHART I.—Curve of blood-sugar levels during glucose-tolerance tests before and after thyroidectomy on a patient with hyperplastic toxic goiter.

As illustration, here are three fairly representative glucose-tolerance charts from our series in thyrotoxic patients. The customary technique was followed: First taking a fasting blood sugar (venous), then administering 75 gm. of glucose by mouth, then taking blood sugar at ½-, 1- and 2-hour intervals. It will be noted there is considerable variation in the basal rates of these patients, both before and after operation.

One of the most interesting observations bearing on this subject has been made by Marks[8] of Dale's laboratory. He found that a

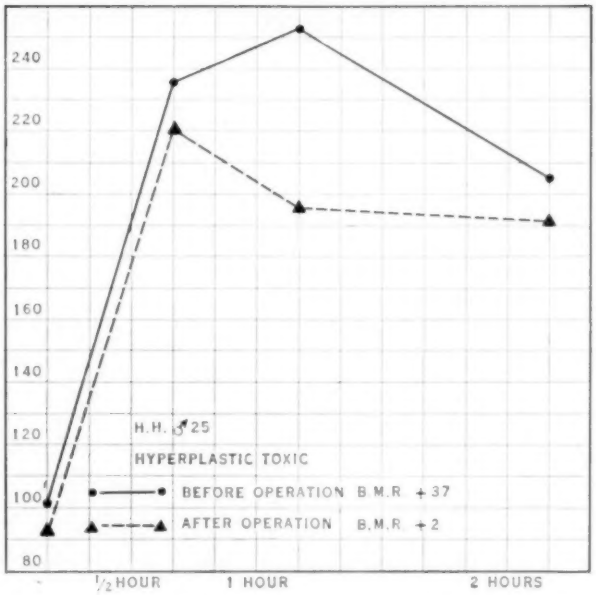

CHART II.—Curve of blood-sugar levels during glucose-tolerance tests before and after thyroidectomy on a patient with hyperplastic toxic goiter.

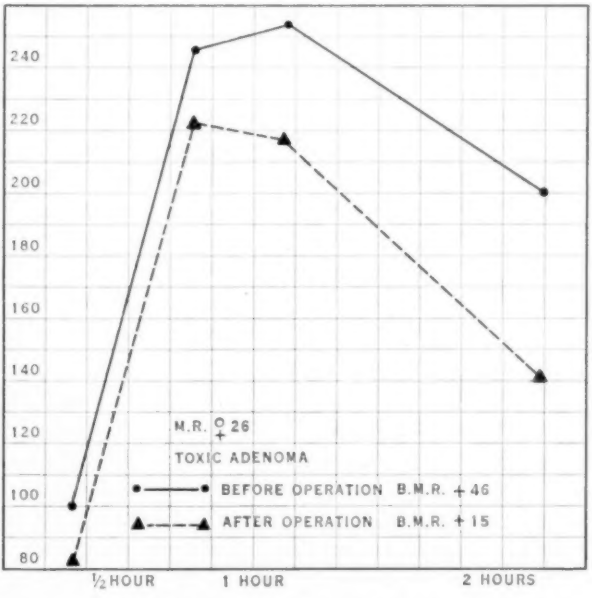

CHART III.—Curve of blood-sugar levels during glucose-tolerance tests before and after thyroidectomy on a patient with toxic adenoma of the thyroid.

secondary hyperglycemia followed injections of glucose or small doses of insulin to rabbits which had been fed thyroid extract, but whose livers still contained glycogen. However, when thyroid extract was fed to the point of depletion of the liver glycogen a small dose of insulin or an injection of glucose produced a fatal hypoglycemia.

The observation of Marks, when coupled with that of Bodansky,[9] is of considerable importance. Bodansky noted that thyroxin administered to sheep caused a rise in the blood sugar. The question naturally arises, from whence does this increase in blood sugar come? If we accept the explanation of Cori, it can come only from the liver. Cori's experiments have proven that muscle glycogen is changed to lactic acid which must be synthesized in the liver to liver glycogen, before it can be mobilized to increase the blood sugar. On the other hand, liver glycogen when mobilized is converted into glucose. Thus the liver is the sole direct source of the blood sugar. It is well known that a hepatectomy causes a fatal hypoglycemia.

These observations, in themselves so pertinent to our theme, are of even greater importance when correlated with those of Denis, Aub and Minot,[10] who found that, although a fasting hyperglycemia was rarely associated with hyperthyroidism, alimentary hyperglycemia was observed in every instance.

It would thus seem that thyroid extract or hyperthyroidism may cause some increase in the blood sugar; that they cause a diminution in the glycogen stores of the liver and, furthermore, the evidence at hand suggests that in hyperthyroidism the liver is not able to store glycogen after feeding as easily as is the normal liver.

We are faced with the fact that even though the liver is glycogen poor, glycogen storage is reduced after feeding. The importance of realizing these facts lies in the relationship which exists between the liver and blood sugar replenishment. Even though the blood sugar may be normal, the liver glycogen supply may be extremely low. As long as the liver contains any available glycogen the blood sugar will be maintained. However, should a crisis demand additional sugar over and above the available supply, hypoglycemia can then readily occur.

One cannot state with any degree of assurance the exact mechanism involved in the hyperglycemic response to the increased secretion of thyroxin. Shpiner[11] believes that the hyperglycemia and glycosuria which follow thyroid feeding are probably due to the increased basal metabolic rate which is associated with thyroid feeding. It is his contention that the thyroid influences carbohydrate metabolism indirectly. Whether the effect is direct or indirect, anyone who has conducted thyroid feeding experiments on the dog will have recognized that the thyroid fed animals are less tolerant to starvation than the control animals.

Abderhalden and Wertheimer[12] reported that thyroxin or thyroid substance administered to dogs, rabbits, guinea pigs, rats and mice caused a reduction in the glycogen content of the animal. This was especially marked in the liver. As the feeding is continued the carbohydrate stored in the liver is totally used up and the blood sugar falls. Associated with these changes, if the feeding is maintained, is a rise in the body temperature, an increase in the carbon dioxid output and death.

One might go on indefinitely reviewing evidence which suggests the very close relationship which the thyroid gland has to carbohydrate metabolism. We are convinced on the basis of the investigations of others and of ourselves that a rational, postoperative therapy must take into consideration this relationship.

For some years glucose has been used in the postoperative period, but not very intelligently. Frequently it was given by rectum, a method we now know to be totally ineffectual. There is no real reason why it cannot be given by mouth, except that one cannot control the rate of absorption. When given intravenously numerous precautions are necessary.

As usually administered intravenously a large amount of glucose has been introduced rapidly into the circulating blood. It is surprising that many surgeons have failed to ascertain the amount of glucose which pours through the kidneys by this method. In 1917 Wilder[13] showed that while the normal individual can take care of 0.8 gm. of glucose per kilogram of body weight per hour when given intravenously, the patient with hyperthyroidism develops glycosuria when as much as 0.6 gm. of glucose per kilogram of body weight per hour is injected. This would indicate faulty glucose assimilation.

Another factor which many investigators and clinicians have not considered as carefully as they should is the state of dehydration which exists in so many of these cases. Dehydration and glycogen content of the liver bear a direct relationship. The liver, even if supplied glucose, will not store it if sufficient fluids are not available. It is of the utmost importance, therefore, to correct dehydration at the same time that an attempt is being made to correct glycogen depletion of the liver. It is much more important to correct dehydration in these cases than it is to correct blood reaction.

For these reasons we are absolutely opposed to the administration of glucose solutions rapidly or in too high concentrations. We have found that a 5 to 10 per cent solution is, as a rule, more satisfactory. Furthermore, we believe that the slow intravenous continuous drop has many advantages over the other methods.

It permits the addition of fluid at a rate at which the tissues, which normally take a part in the storage of water, can accommodate it. Thus other vital cells which normally take little part in water metabolism are not called into action. It lessens the danger of

"speed shock," so that reactions are rare. It permits of the very slow administration of glucose at a controllable rate, so that the injected glucose is utilized both in sparing the body stores and furthermore by supplying additional amounts for storage. It is only rarely that glycosuria appears when glucose is administered in this way. And at the same time it permits one to introduce fluid and food in predetermined amounts, since by regulating the rapidity of the drip one can calculate the total amount of fluid and glucose which can be given in a 24-hour period.

I am convinced that we have less alarming reactions and have saved lives since we adopted this technique. The following records are cited as illustrations of the effect of glucose solution, properly administered, in patients with severe postoperative crises.

Case Reports. CASE 1.—D. G., aged 24 years, was admitted to the Thyroid Clinic of the University Hospital, February 12, 1931.

History. Her illness covered a period of 18 months, during which time nervousness, emotional instability, tachycardia, tremors, excessive fatigue, frequent headaches and sleeplessness had progressively increased. She had lost 51 pounds in weight. For 3 months she had noticed enlargement of the thyroid and exophthalmos. At that time she was hospitalized elsewhere for 3 weeks, where she was given iodin and kept at rest, with no improvement.

Previous Medical History. Pneumonia in childhood; frequent attacks of tonsillitis; tonsillectomy in her twelfth year; appendicitis with appendectomy when 18 years of age.

Social History. Married 3 years; deserted by husband after 1 month. One uneventful pregnancy 20 months ago.

Examination. Blood pressure was 146 systolic and 70 diastolic. Pulse, 130. Flush over face, neck and thorax. Whole body surface warm and moist. Marked exophthalmos. Diffuse firm thyroid enlargement. Heart action pathologically vigorous. Marked tremor of fingers and tongue. Quadriceps weakness; tendon reflexes hyperactive.

Electrocardiogram. Simple tachycardia.

Basal Metabolism. In a period of 3 weeks: 82, 60, 54, 63.

Pre-operative Medication. Lugol's solution, 15 minims; sodium bromid, 15 gr. luminal, 1½ daily, from February 13 to March 5, 1931.

Operation. March 5, 1931. Right lobectomy. Two hours before she received 0.6 gram of sodium amytal and 15 minutes before morphin sulphate, $\frac{1}{6}$ gr. and atropin sulphate, $\frac{1}{70}$ gr. These were supplemented by light nitrous oxid anesthesia. Blood sugar immediately before operation was 76 mg. per 100 cc. and a half hour after operation 104 mg.

Continuous venoclysis glucose, 10 per cent, was started immediately.

8 hours after operation: Temperature, 102°; pulse, 152; respiration, 32.

20 hours after operation: Temperature, 102°; pulse, 160; respiration, 30.

24 hours after operation: Temperature, 101.3°; pulse, 144; respiration, 32; blood sugar, 99 mg.

During the first 24 hours the fluid intake was 2120 cc., including 1500 cc. of 10 per cent glucose. Medication included Lugol's solution, 3 cc.; sodium amytal, 9 gr. and morphin, ½ gr.

Thirty-two hours: Temperature, 101°; pulse, 184; respiration, 32. Patient delirious. In one of the few moments she was not being watched she got out of bed. Continuous venoclysis resumed.

Forty-eight hours: Temperature, 101°; pulse, 160; respiration, 26.

During the second 24 hours the patient received 2000 cc. of 10 per cent glucose; 1140 cc. water; sodium amytal, 18 gr; Lugol's solution, 4 cc., and morphin sulphate, 1 gr. Venoclysis discontinued.

60 hours: Temperature, 103°; pulse, 148; respiration, 26.
72 hours: Temperature, 100°; pulse, 128; respiration, 32.
96 hours: Temperature, 100°; pulse, 104; respiration, 24.
120 hours: Temperature, 98°; pulse, 100.

Comment. This case was recognized as a bad operative risk. Her basal metabolic rates were high and responded only moderately to treatment; she had lost much weight; she had been sick for 1½ years and was not relieved by rest and iodin. It was a matter of no surprise when she developed a crisis marked by great restlessness, delirium and tachycardia. I am reasonably confident, judging from my experience with other cases, that without the continuous glucose venoclysis the patient would not have survived. In this, as in the second case, the tendency to hyperpyrexia seemed to be controlled by the specific glucose therapy.

April 3, 1931. The subsequent convalescence was uneventful. One month after the operation the patient was quite composed, she had gained 3 pounds, was much stronger and had no palpitation.

Once a crisis is established the patient usually succumbs within 48 hours. Only 2 of our cases have lived beyond that time.

Case 2.—M. S., aged 30 years, was admitted to the Thyroid Clinic of the University Hospital, January 12, 1931.

History. For 2½ years she had suffered with nervousness, weakness, palpitation, dyspnea, emotional instability and exophthalmos. She had lost 32 pounds. Five weeks after the onset of her illness she had a thyroid operation elsewhere. Her goiter was not reduced in size and all of the signs and symptoms of thyrotoxicosis were aggravated, becoming progressively worse until admission.

Past Medical History. Quinsy 9 years ago followed by tonsillectomy.

Family History and Social History. Inconsequential.

Examination. Blood pressure was 200 systolic and 110 diastolic; pulse, 130.

Marked exophthalmos, very restless, face flushed, skin warm and moist. Marked bilateral thyroid enlargement. Heart enlarged; systolic apical murmur. Marked tremors of fingers and quadriceps weakness.

White blood cells, 9600. Fractional gastric analysis showed no free hydrochloric acid.

Basal Metabolism. Before operation: 47, 32, 30.

Pre-operative Treatment. Lugol's solution, 16 minims; sodium bromid, 1 gram luminal, 1½ gr. daily for 19 days.

Operation. January 31, 1931. Avertin, 5.2 cc., was given 1 hour before a right lobectomy under light nitrous oxid anesthesia. The pulse was 148 at the start and 120 at the end of the operation. At no time was there free bleeding. When she arrived at the ward the blood pressure was 162 systolic and 98 diastolic; temperature, 98°; pulse, 152; respiration, 32.

Twelve hours after the operation the temperature rose to 102.3° and the pulse to 192. At the time I did not anticipate she would survive more than a few hours. She was given 400 cc. of 5 per cent glucose, and her condition improved almost immediately. The crisis seemed under control.

Twenty-four hours after the operation a second crisis seemed impending.

The temperature which had returned to normal rose to 101° and the pulse to 186. She became cyanotic and again the end seemed not far off. Continuous intravenous medication with 5 per cent glucose was begun. In the second 24 hours she received 3500 cc. of a 5 per cent glucose and again there followed a degree of improvement which encouraged us to believe the crisis had been stemmed.

Unfortunately at this time it was evident the patient was developing pneumonia to which she eventually succumbed, but not until 86 hours after the operation. The necropsy revealed a status thymolymphaticus, bilateral bronchopneumonia and a right lobar pneumonia.

Comment. It is my belief that had the patient not developed pneumonia she would have survived. At all events she did not succumb within the first 48 hours as did most other patients in crisis, but lived 3½ days. I am inclined to believe her life was prolonged by the liberal use of glucose.

Just what causes these crises is as yet a matter of speculation. That glucose helps to tide the patient over a very critical period we feel sure. Perhaps the entire process is one of disturbed carbohydrate metabolism, though the problem may be more complicated. Perhaps it is also associated with an acute thyroid or parathyroid dysfunction or both over which glucose may have a moderating influence. I realize we have been delving in matters controversial, but if progress is to be made we must permit ourselves to indulge in speculation. In some particulars we have gone beyond the speculative field as to carbohydrate metabolism and as to the relation of the thyroid to pancreas and liver.

Summary. 1. There is both experimental and clinical evidence to prove that hyperglycemia is associated with hyperthyroidism.

2. Hypertrophy of the islands of Langerhans has followed thyroidectomy and *per contra* in exophthalmic goiter with glycosuria there is a decrease in these islands.

3. Hyperthyroidism exhausts the glycogen stores in the liver, the liver seems to be the only source of blood sugar.

4. A crisis may demand sugar over and above the available supply and may precipitate a fatal hypoglycemia.

5. If we recognize a relationship between thyroid dysfunction and carbohydrate metabolism, glucose properly administered may be a rational agent in the management of postoperative crises.

REFERENCES.

1. Best, C. H., Dale, H. H., Dudley, H. W., and Thorpe, W. V.: Nature of Vasodilator Constituents of Certain Tissue Extracts, J. Physiol., 1927, **62**, 397.

2. Schliephake, E.: Zur Kenntnis des Schilddrüseneinflusses auf die Wirkung vegetativer Gifte, Arch. f. exper. Path. u. Pharmakol., 1928, **132**, 349.

3. Bowman, K. M., and Kasanin, J.: Sugar Content of Blood in Emotional States, Arch. Neurol. and Psychiat., 1929, **21**, 342.

4. Holst, J.: Glycosuria and Diabetes in Exophthalmic Goitre, Acta med. Scandinav., 1921, **55**, 302.

5. Falta, W.: Weitere Mitteilungen über die Wechselwirkung der Drüsen mit innerer Sekretion, Wien. klin. Wchnschr., 1909, **22**, 1059.

6. Rosenberg, M.: Blutzuckerstudieren: 2. Die alimentäre Hyperglykamie bie Gesunden, Diabetikern und Basedowischen, Arch. f. exper. Path. u. Pharm., 1922, **93**, 208.

7. John, H. J.: Carbohydrate Metabolism in Hyperthyroidism, Endocrinology, 1927, **11**, 497.

8. Marks, H. P.: Effect of Thyroid Feeding on Sugar Tolerance, J. Physiol., 1925, **60**, 402.

9. Bodansky, A.: Antagonistic Effects of Insulin and Thyroxin, Proc. Soc. Exper. Biol. and Med., 1922–1923, **20**, 538.

10. Denis, W., Aub, J. C., and Minot, A. S.: Blood Sugar in Hyperthyroidism, Arch. Int. Med., 1917, **20**, 964.

11. Shpiner, L. B.: Further Studies on the Alleged Interrelationship of Pancreas and Thyroid, Am. J. Physiol., 1927, **83**, 134.

12. Abderhalden, E., and Wertheimer, E.: Studien über die Wirkung des Thyroxins auf den tierischen Organismus und insbesondere auf die Wärmeregulation des Gleichwarmblüters, Arch. f. d. ges. Physiol., 1928, **219**, 588.

13. Wilder, R. M.: d-Glucose Tolerance, Arch. Int. Med., 1917, **19**, 311.

THE EFFECT OF EPHEDRIN UPON THE HUMAN STOMACH AS DETERMINED ROENTGENOLOGICALLY.

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Few roentgenologic observations concerning the effect of ephedrin upon the human stomach* have been made. These reports are conflicting.

Pollak and Robitschek (1926),[1] using the roentgenologic method, noted that gastric peristalsis and the rate of gastric emptying were increased after oral ingestion (20 drops of 10 per cent solution), but were unable to venture an opinion whether this was due to a direct stimulation of the gastric musculature or a reflex action as a result of the irritant effects on the mucosa. Marcou and Savulesco (1928)[2] worked with this same problem, employing a different method. Ephedrin was injected intravenously in varying amounts after the subject swallowed a balloon which was connected with a water manometer. Doses of 0.1 to 20 mg. produced an inhibition of gastric movements, followed by exaggerated movements in the case of the 20-mg. dose. Doses below 0.1 mg. either produced no effect or transitory contraction only. Scholtz and Mohos (1929)[3] studied 22 cases roentgenologically, examining each case routinely without the drug for control purposes and repeating the test with the drug (0.05 gm. subcutaneously) on the following day. They

*Throughout this study the duodenal bulb and stomach have been considered as a single functional or physiologic unit, and the expression, stomach, should be interpreted by the reader as having this connotation.

found a constant inhibiting effect on tone and peristalsis, with prolongation of emptying time.

Thus a considerable difference in opinion arises. These opinions vary from a purely stimulative effect to one of pure inhibition.

Several attempts have been made to solve this problem by studying the action of ephedrin experimentally on animals, but here also much of the evidence is conflicting. This is particularly true of the isolated muscle preparation. With the organ *in situ*, few observations have been made. These, in general, suggest a relaxation with inhibition of peristalsis (Kinnaman and Plant, 1927[4]; M'Crea and MacDonald, 1928[5]). Chen and Schmidt (1930)[6], after an excellent summary of these effects, write the opinion: "So it is very evident that the effects of ephedrin upon movements of the gastrointestinal tract *in situ* appear to be much more nearly like those of epinephrin than in the case when two agents are tested upon isolated muscle preparations." As Chen and Schmidt add, it is the effects obtained with the organ *in situ* which are of therapeutic or clinical importance. It was believed by the present writer that roentgenologic observations were valuable in a study of this type because it permitted the study of the effects with the organ *in situ* without the introduction of abnormal stimuli incident either to operation or anesthesia.

Antispasmodics have long been used by the roentgenologist in his gastrointestinal work. Atropin has been used chiefly in this respect, and by many was believed to possess diagnostic significance in the differentiation of functional or reflex spasm from that due to an intrinsic lesion. More recently, Holmes and Dresser (1928)[7] have used amyl nitrite to relax spasm. Its action was found to be irregular, particularly in cases of pylorospasm. Ephedrin, though now a well-known antispasmodic, has not been used by roentgenologists in studying the gastrointestinal tract.

The present study was undertaken to: (*a*) Determine the effect of ephedrin on tone, peristalsis and spasm of the stomach; (*b*) study its effects comparatively in stomachs with and without local disease; (*c*) compare its objective effects with atropin. The physiologic action of atropin is produced, of course, in an entirely different way than in the case of ephedrin, the former producing relaxation through the inhibition of the parasympathetic while ephedrin appears essentially sympathicomimetic (Chen and Schmidt, 1930[6]).

Method. Fifty-eight cases were studied before and after the oral administration of ephedrin and 39 cases before and after the subcutaneous injection of atropin. The repeat examination with ephedrin or atropin was always made on the same day and within 0.5 hour after the first examination. This was considered a necessary prerequisite, since normal stomachs vary markedly from day to day in tone and peristalsis and in the presence or absence of spasm. The failure to take this time factor into account will result

in faulty deductions concerning the influence of any drug upon the stomach and is an objection to the study of the effects of atropin after oral administration, since considerable time must elapse before an individual can be safely atropinized by the oral method. Many types of spasm are transitory, and the disappearance of spasm on a second examination should not be taken as evidence that any drug administered between the two examinations produced the effect observed, if a considerable time elapses between the first and second examinations.

Ephedrin possesses this great advantage, that the physiologic effect of the drug is obtained within a matter of minutes after oral ingestion. Usually 30 minutes were sufficient, though many of the cases were followed longer (1 to 2 hours) in order to make several sets of observations on the same case. The dose of ephedrin varied from 50 to 150 mg. The drug was the natural product of Ma Huang manufactured by Eli Lilly & Company and by the Abbott Laboratories. While there are 6 isomers of ephedrin, and the intensity of the physiologic effects vary according to the isomers used, only 2 of these (l-ephedrin and d-pseudoephedrin) occur in the natural product (Chen, Wu and Henriksen, 1929[8]). Both of these are known to exert a pressor effect (cats), the former showing the more pronounced effect. Both are reported by Chen and his associates to have an inhibiting effect on the smooth muscle of the intestines of the rabbit. The natural product, therefore, would appear to be satisfactory for a study of this type; in fact, many of the artificially prepared isomers would probably not be as satisfactory if the pressor effect be accepted as a reliable guide. The natural drug is mostly l-ephedrin, and this is known to be very active, physiologically exerting a pressor effect approximately 35 times as great as the weakest isomer.

In order to insure the employment of an adequate physiologic dose, blood pressure and pulse rate were taken before and after the administration of ephedrin, with the patient recumbent. If neither of these were affected by the drug the dose was repeated until the pressor effect was obtained. An increase in blood pressure or pulse rate of 15 was the smallest elevation accepted as indicative of the pressor or the cardiac stimulant effect.

The cases were selected during the course of routine gastrointestinal examinations usually because of the presence of spasm, though in many instances spasm was absent, and the drug was administered to determine the effect on peristalsis and tone. A total of 97 cases were studied, of which 58 were given ephedrin and 39 atropin. The subjects were all adults, varying in age from 20 to 73 years.

Results. *Action of Ephedrin on Tone, Peristalsis and Spasm of Normal Stomachs Free of Organic Disease.* Out of the total of 58 cases studied 32 cases were found to be free of local disease.

Thirteen of these were studied with particular attention to peristalsis and tone. In 11 cases peristalsis was definitely decreased, while in 2 no demonstrable change was apparent. In all cases where peristalsis was diminished the tone was likewise decreased. Figs. 1 and 2 show the usual reaction obtained in normal stomachs.

Twenty-one of the 32 cases were studied because of the presence of spasm. Most of these were cases of pylorospasm, though 5 of them showed spasm at a distance from the pylorus affecting the pars media. After ephedrin, 10 out of 15 cases of pylorospasm showed a disappearance of the spasm sufficient in degree to permit the filling of the duodenal cap. In most of these cases, however, the relaxation was not complete and barium passed only in small amounts from the pylorus. The remaining 5 out of 15 cases showed no change, and in several of the cases the spasm appeared to be greater than at the initial examination. Figs. 3 and 4 illustrate the persistence of pylorospasm of the stomach in a young adult (without evidence of a local lesion) after a dose of 150 mg. of ephedrin. This patient showed a very marked pressor effect, but in spite of the fact that the dosage was sufficiently high to produce a decided physiologic reaction, the spasm did not disappear. Of the 5 cases showing spasm elsewhere in the stomach, 4 showed a notable change with practically complete disappearance of spasm.

A typical case of advanced cardiospasm was examined during this series and carefully followed after ephedrinization. The ephedrin exerted no observable effect on the spasm of the esophagus, though the ephedrin effect on the stomach (diminished peristalsis and tone) was evident.

Thus, in summary it is to be noted that ephedrin commonly decreases tone and peristalsis of the normal stomach or of the stomach free of organic disease. In this series there was no evidence of a stimulating effect either in tone or peristalsis. Ephedrin, on the other hand, does not appear to be as effective in relaxing pylorospasm, though in many cases (two-thirds) a partial effect is obtained. In a single case of cardiospasm no effect on the spasm was apparent.

Action of Ephedrin on Tone, Peristalsis and Spasm in Cases of Organic Disease. The chief intrinsic lesion (lesion within upper gastrointestinal tract) in these cases was duodenal ulcer (14 cases); a few cases of extrinsic lesions, such as periduodenal adhesions (7 cases), cancer of gall bladder (1 case) and cancer of esophagus (1 case) are included. Three cases were of undetermined origin. Eleven of the 14 cases of duodenal ulcer were studied with particular attention to changes in peristalsis and tone. In 6 of these there was evidence of a decrease in peristalsis and tone, the others showing no perceptible effect. Seven cases of duodenal ulcer showed persistent spasm, chiefly pylorospasm, and in only 2 of these cases was any change noted after ephedrin. A typical incisura of the duodenal cap due to the presence of a local ulcer was followed in this

group. Figs. 5 and 6 illustrate the persistence of the spasm of the circular muscle fibers at the level of the ulcer after a dose of 125 mg. of ephedrin.

TABLE 1.—RESULTS OBTAINED ON TONE, PERISTALSIS AND SPASM AFTER THE USE OF EPHEDRIN.

Type of lesion.	Effect on tone and peristalsis.			Type of spasm.	Effect on spasm.		
	No. of cases.	Relax. prod.	No change.		No. of cases.	Relax. prod.	No change.
No lesion, 32 cases	13	11	2	Cardiospasm	1	0	1
				Pylorospasm	15	10*	5
				Other spasm	5	4	1
Local lesions: duodenal ulcer, 14 cases	11	6	5	Cardiospasm	0		
				Pylorospasm	6	2	4
				Other spasm	1	0	1
Extrinsic lesions, 9 cases	3	3	0	Cardiospasm	0		
				Pylorospasm	5	1	4
				Other spasm	1	0	1
Undetermined, 3 cases	1	0	1	Cardiospasm	0		
				Pylorospasm	1	0	1
				Other spasm	1	1	0
Totals, 58 cases	28	20	8	....	36	18	18

* Partial.

The extrinsic lesions (9 cases) were similarly studied. Three were followed for changes in tone and peristalsis, with a positive result in all 3. Five cases of pylorospasm were followed in this group and in only 1 case was any change apparent. A typical incisura of the stomach was followed in this group and ephedrin was without effect.

Summarizing, relaxation after ephedrin in the presence of a local intrinsic lesion occurs in about one-half of the cases. This is considerably less than noted in cases in which the stomach and bulb show no lesion. It is probable, however, that the use of ephedrin possesses no diagnostic value in the differentiation of intrinsic and extrinsic lesions, though the high tone and spasm tend to persist longer and are modified less by ephedrin in cases where local disease is present.

Blood-pressure readings and pulse rates were recorded on approximately two-thirds of the cases in order to insure giving the drug in adequate doses. These were of interest in showing that usually either blood pressure became elevated or the pulse rate increased, but it was uncommon for both the blood pressure and pulse rate to increase markedly (above 15 points) in the same subject. Only 5 cases in this series showed both an elevation of blood pressure and heart rate exceeding 15. In fact, in several of the cases the pulse was actually slowed while the blood pressure became elevated.

This slowing of the pulse is probably compensatory to the pressor effect.

Pronounced reactions to the drug at the dosages given were distinctly uncommon. Evidence of slight toxic effects was found in approximately 15 per cent of the cases. These effects consisted chiefly of nausea and palpitation. In some of the cases direct questioning was required to elicit information concerning these reactions. While nausea was one of the common slight reactions, vomiting occurred in only 1 case. Two cases showed a transitory arrhythmia. In general, reactions were absent or minimal in those cases where the pressor effect of the drug was not marked. In only 1 case was a violent reaction obtained. This occurred in a nervous young Italian, of rather slender build. His blood pressure rose from 122 systolic, 80 diastolic to 205 systolic, 110 diastolic at the end of the first hour, reaching a peak of 220 systolic, 115 diastolic at the end of the second hour. Marked nausea and a severe pounding headache, the throbbing character of which made the patient aware of each cardiac systole, were the outstanding features. There was some retching, but only a few cubic centimeters of bile-stained material were vomited. His blood pressure fell during the course of the third hour and reached a level of 165 systolic, 90 diastolic at the end of 2.75 hours, and as it fell the reaction diminished. His pressure on the following morning was normal (120 systolic, 78 diastolic). This patient was given the drug because of the presence of pylorospasm, and it is a noteworthy fact that the drug not only failed to remove the spasm, but the reaction appeared to make the spasm more pronounced, the latter affecting the duodenal cap as well as the pyloric end of the stomach. (Fig. 4.)

Atropin Series. In the following series 39 individuals were examined prior to the injection of 1.5 mg. of atropin subcutaneously, and after the elapse of approximately 25 to 30 minutes were re-examined to observe changes. The subcutaneous route was employed in order to avoid, as much as possible, the time factor. In order to insure employing atropin in proper physiologic dosage the pulse rate and dryness of mouth were followed. All cases at the time of the second examination showed definite dryness of the mouth and usually an increase of 20 to 30 in pulse rate. Exceptionally an increase of 40 or more occurred.

Action of Atropin in Cases Showing No Local Lesion. Twenty, or approximately one-half, fell in this group. Five cases of markedly active peristalsis were followed, and in 4, after atropin, peristalsis and tone were much diminished. In 8 cases of pylorospasm relaxation of spasm was noted in only 3. Five cases of cardiospasm were followed without noting any effect. Seven cases of spasm of stomach proper showed a definite change in only 3. That atropin may fail to relax spasm of a reflex character in the absence of any local lesion is well shown by the detailed study of a case of

FIG. 1. Before ephedrin.

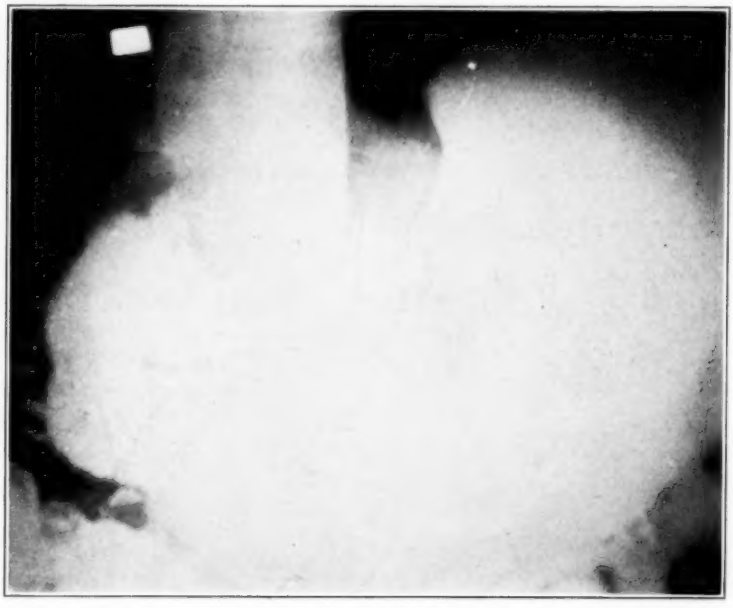

FIG. 2.—After ephedrin.

FILMS OBTAINED BEFORE AND AFTER EPHEDRIN ILLUSTRATING THE USUAL RELAXATION OBTAINED BY THE DRUG IN THE NORMAL STOMACH.

H. M., aged 38 years, male, entered with a complaint of lower abdominal pain of 4 years duration not related to meals. Physical examination was negative except for a few carious teeth. The gastrointestinal series showed a normal stomach and duodenum. Twenty minutes after 100 mg. of ephedrin orally, the tone of the stomach diminished. Note, however, that faint waves of peristalsis can be identified over the lower end of the stomach. It was a common finding to note that in the normal stomach peristalsis was commonly diminished rather than completely abolished.

FIG. 3.—Before ephedrin.

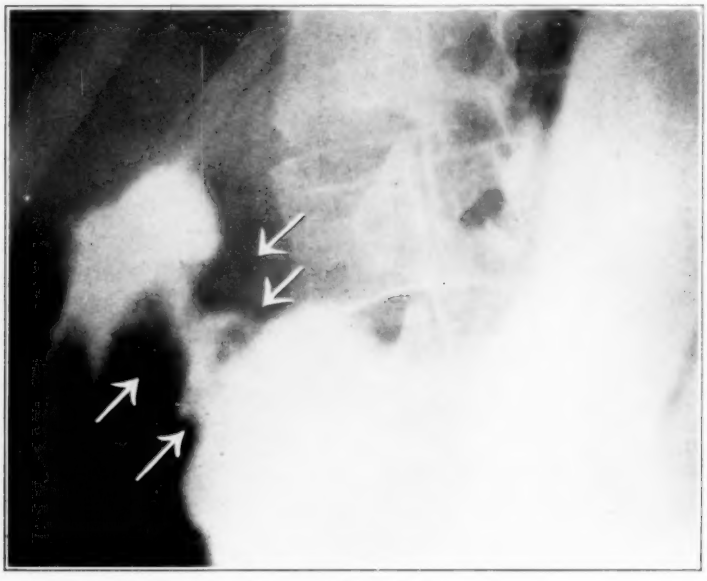

FIG. 4.—After ephedrin.

CASE OF PYLOROSPASM NOT RELIEVED BY EPHEDRIN.

E. N., male adult, aged 38 years, gave a history of vague distress after meals, varying in time but commonly immediately after eating. The physical examination was essentially negative. The gastrointestinal series showed no evidence of a local lesion. There was persistent spasm affecting the pyloric end of the stomach. A large oral dose of 125 mg. failed to relax this spasm though the drug produced a marked pressor effect (elevation of systolic pressure of 100). Note that the contraction of the lower stomach appears more marked after the ephedrin and that the base of the cap has become similarly affected.

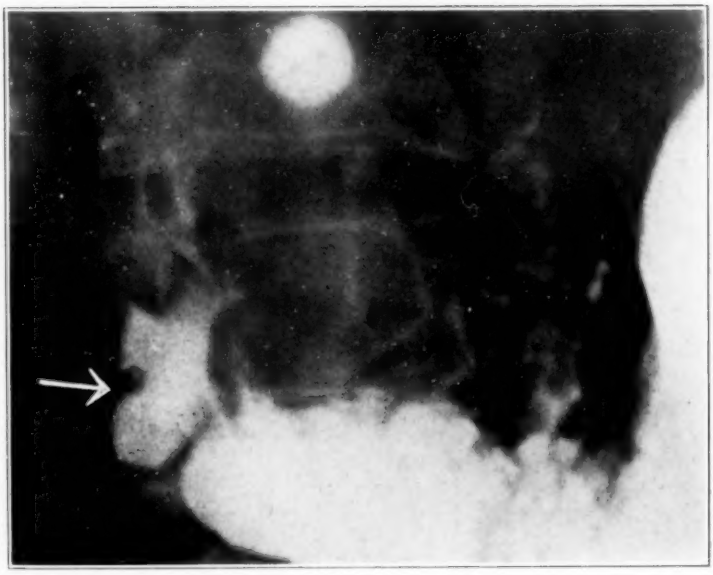

FIG. 5.—Before ephedrin.

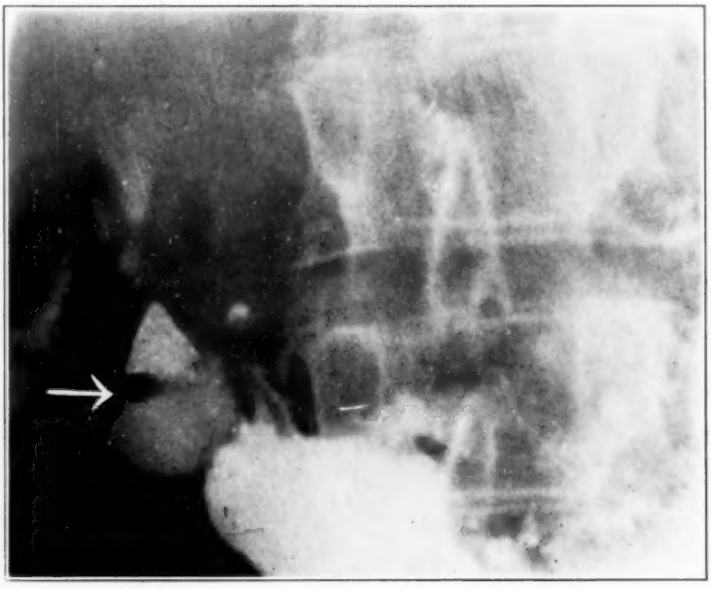

FIG. 6.—After ephedrin.

ILLUSTRATING THE PERSISTENCE OF THE INCISURA OF DUODENAL ULCER AFTER EPHEDRINIZATION.

J. S., male, aged 52 years, gave a twenty-year history of postprandial distress relieved by food and soda. Gastrointestinal examination showed a persistent deformity of the lesser curvature with a spastic incisura of the greater curvature of the cap. Ephedrin sulphate (125 mg. orally) failed to relax the spasm of the cap. The patient died with cerebral hemorrhage one week later. At autopsy the diagnosis of duodenal ulcer was verified.

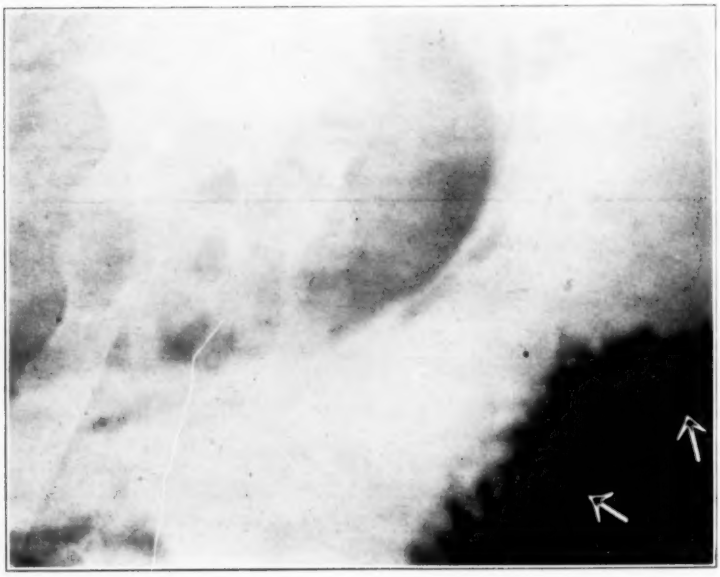

FIG. 7.—Before atropin.

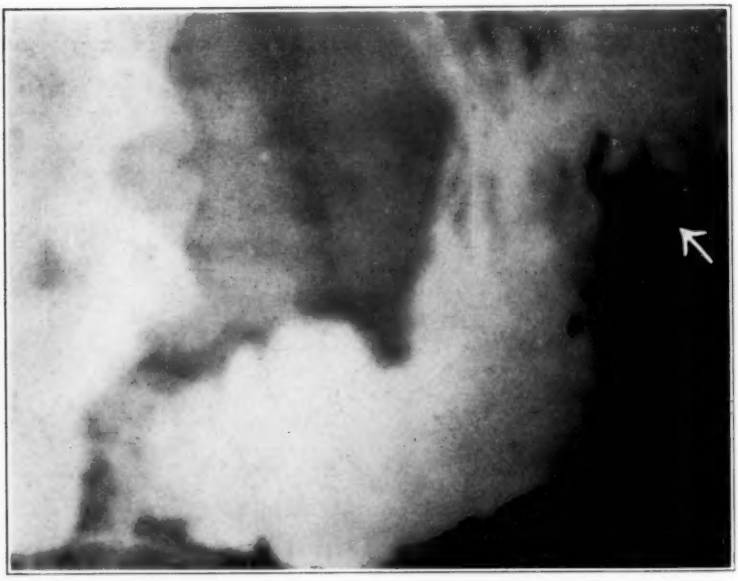

FIG. 8.—After atropin.

FIG. 9.—Following day.

ILLUSTRATING FAILURE OF ATROPIN TO RELAX REFLEX SPASM.

E. R., adult male, aged 47 years, gives long history of drug addiction and of syphilis of the central nervous system. He was examined roentgenologically because of history of spells of nausea and vomiting, only relieved by morphin. Gastric examination made without motility studies at a time when the patient was experiencing an attack showed a large defect on the greater curvature over which no peristalsis passed and which persisted after atropin (1.5 mg.), subcutaneously. Large doses of morphin gave only symptomatic relief. An examination on the following day revealed an entirely normal stomach with the defect absent and with normal peristalsis passing over this area. He was operated upon one week later. At this time an essentially normal stomach was found.

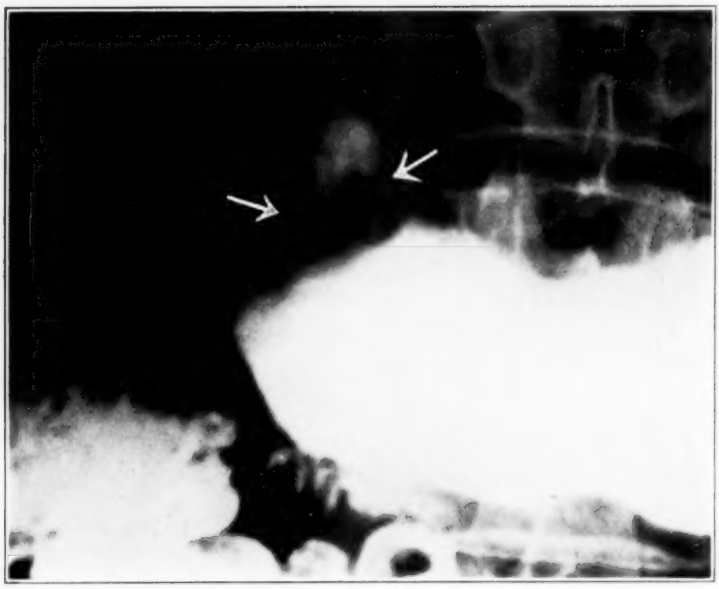

FIG. 10.—Before atropin.

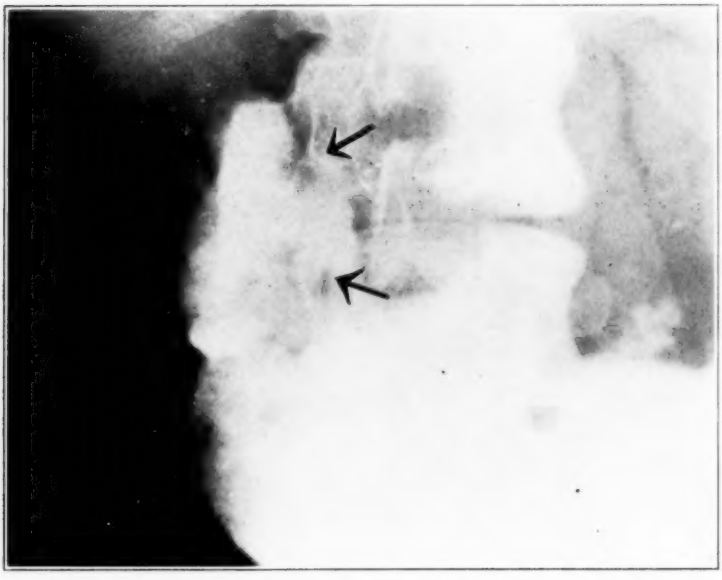

FIG. 11.—After atropin.

ILLUSTRATING FAILURE OF ATROPIN TO RELAX SPASM RELATED TO AN EXTRINSIC LESION.

(Chronic Cholecystitis with Cholelithiasis).

C. B., an adult male, aged 41 years, gave a history of lower abdominal pain of 2 years duration. At the gastrointestinal examination a persistently irregular, spastic cap was noted. After 1.5 mg. of atropin subcutaneously, the cap was followed carefully, fluoroscopically and by films. Large, irregular defects persisted in the cap. Peristalsis of the stomach was not affected. Three days after the gastrointestinal examination, a gall bladder with thickened walls and with 236 faceted stones varying in size from 0.5 to 1.5 cm. in diameter was removed at operation. The stomach and duodenum showed no evidence of pathology.

gastrospasm occurring in a patient addicted to the use of morphin, with cerebrospinal lues. (Figs. 7, 8 and 9.) This case was examined both before atropin and after atropin and later after morphin. Neither of these two drugs produced any observable result, though the morphin relieved the pain of which the patient was complaining. That this defect was entirely spastic was proved by observations on the following day, when an entirely normal gastric contour was outlined, and by subsequent operation when no pathology relating to the stomach was found.

TABLE 2.—RESULTS OBTAINED ON TONE, PERISTALSIS AND SPASM AFTER THE USE OF ATROPIN.

Type of lesion.	Effect on tone and peristalsis.			Type of spasm.	Effect on spasm.		
	No. of cases.	Relax. prod.	No change.		No. of cases.	Relax. prod.	No change.
No lesion, 20 cases	5	4	1	Cardiospasm	5	0	5
				Pylorospasm	8	3	5
				Other spasm	7	3	4
Local lesions: duodenal ulcer, 12 cases; gastric carcinoma, 2 cases; gastric ulcer, 1 case	8	5	3	Cardiospasm	0		
				Pylorospasm	10	2	8
				Other spasm	5	1	4
Extrinsic lesions, 4 cases	4	1	3	Pylorospasm	1	1	0
				Other spasm	1	0	1
Totals, 39 cases	17	10	7	....	37	10	27

Action of Atropin in Cases With Local Lesion. Twelve cases of duodenal ulcer were studied and 8 of these showed marked hyperperistalsis affording us a good opportunity to follow this effect. Five out of 8 showed notable diminution of peristalsis and tone. The remaining 3 were unaffected, although atropin had been given in physiologic dosage. A case of gastric carcinoma likewise showed no change. Ten cases of duodenal ulcer were selected because of the presence of pylorospasm, and in only 2 cases was a definite positive result achieved. Two cases of duodenal ulcer showed reflex spasm of the stomach which was not affected by atropin. A single case of gastric ulcer showed marked spasm which was unaffected. Similarly,[2] cases of gastric cancer associated with spasm showed no change after atropinization. Four cases of extrinsic pathology (duodenal adhesions, cholelithiasis and extrinsic mass) were studied. Diminution of peristalsis was noted in only 1. The failure of atropin to relax duodenal spasm in a case of extrinsic pathology (cholecystitis with cholelithiasis) is well illustrated by Figs. 10 and 11. This patient showed unusually deep spasm which greatly deformed the cap, simulating an ulcer. Atropin did not remove this spasm, though operation a few days later proved the

diagnosis of cholelithiasis and demonstrated the absence of pathology in the duodenum.

Summary. Ephedrin accomplishes much the same objective result that is seen after atropinization. Peristalsis and tone became decreased in the vast majority of individuals with normal stomachs after either ephedrinization or atropinization while these effects occur much less frequently if a local lesion is present. While ephedrin was as successful as atropin in this series in relaxing spasm, attention is called to the obvious finding that both of these drugs failed to relax spasm in one-half or more of the cases studied. No case of cardiospasm appeared benefited by either drug, and in cases of pylorospasm it was a common finding to note only partial relaxation. Neither of these two drugs should be accepted as a diagnostic agent in the differentiation of an intrinsic lesion from an extrinsic one with reflex spasm. Both of these drugs relax spasm in the presence of local disease, and it was a very common finding to note the absence of any relaxation after the use of these drugs in stomachs which were obviously entirely normal.

It is quite probable that the impression of the usefulness of atropin in this regard has been gained because at a second examination on a succeeding day cases in which no intrisic local lesion was present did not show spasm, while spasm persisted in cases that had local lesions. This undoubtedly is true, but this present work would indicate that this is due to the time factor rather than any constant action of the drug. It is rare for a normal stomach, free of local lesions, to show the same spasm at the same level on different days.

Conclusions. 1. Ephedrin commonly produces a diminution in peristalsis and tone in the human stomach free of local disease.

2. In relaxing spasm the action of ephedrin is more variable, often failing in cases of pylorospasm in stomachs free of local pathology.

3. In stomachs showing local disease spasm is less often affected by ephedrin and less modified when affected than in normal stomachs.

4. Ephedrin accomplishes much the same objective result that is seen after atropinization, though its mode of physiologic action is different.

5. Neither ephedrin nor atropin should be accepted as a specific diagnostic agent in the differentiation of an intrinsic lesion from an extrinsic one.

6. Both of these drugs may relax spasm in the presence of local organic disease or may fail to relax spasm of a reflex or functional character.

7. If it is desired to relax a stomach in order to study a questionable deformity more readily ephedrinization has the obvious advantage over the use of atropin in that the former can be accomplished in a few minutes by the oral method, permitting the entire study to be finished at one examination.

8. Great emphasis is placed, however, on the value of a second examination on a succeeding day in the study of spasm, since stomachs free of organic pathology rarely show the same spasm at a second examination.

9. These drugs are not effective in the relaxation of cardiospasm, and their action in cases of pylorospasm is variable.*

* I desire to express my thanks to Dr. S. L. Warren for aid in preparing the manuscript.

BIBLIOGRAPHY.

1. Pollak, L., and Robitschek, W.: Ueber die therapeutische Verwendbarkeit des Ephedrins in der inneren Medizen, Wien. klin. Wchnschr., 1926, **39**, 753.

2. Marcou, I., and Savulesco, A.: Motilité de l'estomac sous l'influence de l'ephedrine; considerations sur l'amphotropisme de cet alcaloide, Compt. rend. Soc. de Biol., 1928, **98**, 243.

3. Scholtz, A., and Mohos, E.: Magen-Roentgenuntersuchungen in Ephedrinwirkung, Fortschr. a. d. Geb. d. Röntgenstrah., 1929, **40**, 262.

4. Kinnaman, J. H., and Plant, O. H.: Effect of Ephedrin on Intestinal Contractions in Unanesthetized Dogs, J. Pharm. Exp. Therap., 1927, **31**, 212.

5. M'Crea, E. D., and MacDonald, A. D.: Action of Drugs on Movements of Stomach, Quart. J. Exp. Physiol., 1928, **19**, 161.

6. Chen, K. K., and Schmidt, C. F.: Ephedrin and Related Substances, Medicine, 1930, **17**, 1.

7. Holmes, G., and Dresser, R.: Use of Amyl Nitrite as Antispasmodic in Roentgen Examination of Gastrointestinal Tract, Am. J. Roentgenol., 1928, **19**, 44.

8. Chen, K. K., Wu, C. K., and Henriksen, E.: Relationship Between the Pharmacological Action and the Chemical Configuration of the Optical Isomers of Ephedrin and Related Compounds, J. Pharm. Exp. Therap., 1929, **36**, 363.

A STUDY OF THE FIVE-HOUR DEXTROSE TOLERANCE CURVE IN TREATED DIABETIC PATIENTS.

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The severity of diabetes has often been measured by the degree of hyperglycemia that followed the ingestion of a given amount of glucose. The majority of investigators have confined themselves to a study of the blood sugar curve over a period of 3 hours, although it is generally felt that the persistence of such a hyperglycemia is of more significance than the height.[1,2,3,4,5,6] John[2] thinks the most significant abnormal feature of such a curve may be its failure

to return to the normal fasting level in 3 hours. He considers the absolute height of relative value. Mosenthal[5] also stresses the importance of duration of the hyperglycemia. MacLean and De Wesselow[6] interpret the ability to get rid of the increased blood sugar and return to a normal value within a limited time after sugar ingestion, as the best indication of an effective carbohydrate metabolism. Some investigators only consider a curve that is abnormal for 3 hours diagnostic of diabetes.[3,9] Ohler[10] has wisely stressed the importance of keeping the mild cases under observation. Rabinowitch,[7] who observed the relation of the respiratory quotient and blood sugar following glucose, feels that "the presence of a normal blood sugar 3 hours after glucose ingestion is not a sufficient basis for the diagnosis of a normal carbohydrate metabolism." He found the rate of utilization of glucose in diabetics much below that of the average normal individual, although no perfect correlation existed between this rate and the severity of the disease.

Because of these facts we decided to study the curve over a longer period of time, and to observe the relation of the height of the hyperglycemia to its duration and of these two to the severity of the diabetes. A period of 5 hours was selected, as this is the average interval between meals for most adults. A total of 26 cases was studied. This included 5 normals, 6 mild diabetics, 1 renal glycosuria, 6 moderately severe and 8 severe diabetics. All of the diabetics were patients who were being treated in the Diabetic Clinics of the University and Bellevue Hospital Medical College of New York University, so that the diet, general condition and progress of the patient were observed both before and after the tolerance test. The diet at the time the observations were made was a continuation of the one the patient had been taking, and had been uniform for a period of at least 3 weeks. The carbohydrate, protein and fat values are recorded in the tables. Sweeney[8] has shown that the character of the blood sugar curve in normal individuals can be greatly influenced by the previous carbohydrate, protein or fat content of the diets. When the pancreas had been stimulated by a high carbohydrate diet the carbohydrate mechanism responded more quickly and the hyperglycemia was prevented. The cases on a high fat diet showed a marked decrease in tolerance. A high protein diet caused a mild inability to utilize glucose. None of the patients in our series was on a high fat diet and all but 1 patient received more than 105 gm. of carbohydrate daily.

Procedure. Patients who had run mild, moderate or severe clinical courses were selected for the observations. An effort was made to obtain an equal number of each type. The criteria for these groups based on clinical observations were: (*a*) The starving blood sugars taken during the patient's attendance at the clinic; (*b*) the carbohydrate content of the diet; (*c*) the patient's ability to remain sugar free on the diet; (*d*) the amount of insulin required to

TABLE I.—MILD DIABETICS.

TABLE 1.—MILD DIABETICS.

Case No.	Blood sugar, mg. per 100 cc. Number of hours after taking 100 gm. glucose. Starv.	0.5.	1.	2.	3.	4.	5.	Greatest rise in mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.	Diet at time of curve. Carb., gm.	Prot., gm.	Fat, gm.	Daily insulin, units.	Present diet. Carb., gm.	Prot., gm.	Fat, gm.	Age.	Duration of diabetes.
6	87.3	168.0	160.0	122.7	108.1	64.7	50.7	81.0	2	3.0	Moderate starch			0	Same			46	Indefinite.
7	94.6	90.9	129.8	188.7	125.0	82.0	77.0	98.0	3	10.3	117	53	128	0	Controlled starch			34	7 yrs.
8	92.0	181.0	205.0	137.0	103.0	90.0	88.0	113.0	2	0.4	130	50	120	0	Controlled starch			40	Indefinite.
9	109.0	156.0	198.0 *190.5	173.0	131.0	128.0	113.0	91.0	4	Tr.	116	56	102	0	140	60	102	61	5 yrs.
10	86.9	121.9	134.2 *166.7	128.2	81.3	80.2	82.0	103.6	2	Tr.	50	45	105	0	Controlled starch			68	Indefinite.
13	95.2	333.0	190.5	125.0	85.5	86.9	64.7	237.8	2	Tr.	150	62	112	0	Controlled starch			50	1.5 yrs.

* Blood sugar at 1.5-hour period.

TABLE 2.—MODERATELY SEVERE DIABETICS.

Case No.	Blood sugar, mg. per 100 cc. Number of hours after taking 100 gm. glucose. Starv.	0.5.	1.	2.	3.	4.	5.	Greatest rise in mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.	Diet at time of curve. Carb., gm.	Prot., gm.	Fat, gm.	Daily insulin, units.	Present diet. Carb., gm.	Prot., gm.	Fat, gm.	Age.	Duration of diabetes.
11	93.5	172.0	235.0	254.0	186.0	102.0	78.4	160.5	3	5.5	112	62	120	5	112	62	120	69	?
12	90.0	145.3	200.0	200.4	222.0	181.8	120.9	132.0	4	4.5	112	62	120	0	Not returned			52	?
14	109.0	235.3	253.2	250.0	274.0	183.5	137.9	165.0	5	8.7	112	62	120	10	112	62	120	39	1 yr.
15	125.0	307.5	210.0	222.0	153.0	117.8	80.0	182.5	3	2.6	105	55	101	0	105	55	101	59	5 yrs.
16	148.0	153.8	285.6	350.8	250.7	166.7	121.0	201.0	4	11.0	115	56	102	0	160	58	104	63	5 yrs.
25	125.0	178.6	241.0	173.9	150.0	111.0	74.1	116.0	3	Tr.	112	55	106	0	142	57	95	50	1 yr.

TABLE 3.—SEVERE DIABETICS.

Case No.	Blood sugar, mg. per 100 cc. Number of hours after taking 100 gm. glucose. Starv.	0.5.	1.	2.	3.	4.	5.	Greatest rise in mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.	Diet at time of curve. Carb., gm.	Prot., gm.	Fat, gm.	Daily insulin, units.	Present diet. Carb., gm.	Prot., gm.	Fat, gm.	Present insulin, units.	Age.	Duration of diabetes, yrs.
17	200.0	202.0	303.0	285.5	224.7	211.6	204.0	103.0	5	5.0	159	59	102	0	164	64	107	0	66	13
18	169.0	222.0	242.0	282.0	342.0	274.0	222.0	173.0	5	9.1	115	56	102	0	125	57	103	0	48	3
19	222.0	284.0	306.0	306.0	316.0	322.0	250.0	100.0	5	18.0	112	62	127	40	112	62	127	30	41	3
20	161.3	236.8	286.5	392.0	312.5	253.0	266.6	230.7	5	16.6	126	61	123	20	115	56	100	20	33	3
21	277.7	303.0	350.9	404.0	392.0	377.0	392.0	127.0	5	5.5	106	60	120	45	150	64	150	35	50	3
22	160.0	168.0	281.0	434.0	370.0	333.0	285.0	274.0	5	26.0	172	71	130	6	172	71	130	10	35	1
23	166.7	200.0	290.0	392.5	444.5	357.3	290.0	277.8	5	5.4	140	69	138	20	160	70	156	20	62	1
24	200.0	319.0	495.0	473.0	361.0	273.0	211.0	295.0	5	20.0	115	56	102	34	122	58	104	42	65	2

keep the patient sugar free. The mild group were patients who had all shown normal starving blood sugars, seldom if ever spilled sugar, required no daily dose of insulin and tolerated more than 110 gm. of carbohydrate. The cases selected for this group on these clinical criteria were Cases 6, 7, 8, 9, 10, 13 and 25. The moderately severe group were patients whose starving blood sugars had not always been within the normal range, who spilled sugar after slight dietary indiscretions, who tolerated 100 to 115 gm. of carbohydrate and who required no insulin or only small doses. The cases selected for this group on these clinical criteria were Cases 11, 12, 14, 15, 16, 17 and 18. The severe group were those patients in whom the fasting blood sugar in the clinic had always been above the normal level and who required insulin daily to remain sugar free. The cases selected for this group were Cases 19, 20, 21, 32, 23 and 24.

The patients were instructed to eat nothing after their supper meal and to report to the clinic without eating breakfast. A fasting sample of blood was taken, the patient emptied his bladder and was then given 100 gm. of dextrose dissolved in 300 to 400 cc. of water. Blood samples were taken at periods of 0.5, 1, 2, 3, 4 and 5 hours. The urine was collected during the experimental period and examined for sugar by Benedict's method. The blood proteins were precipitated immediately and the sugar determined by the modified Folin-Wu method.[11]

Results. As a result of the tolerance curves the patients were again grouped into mild, moderately severe and severe groups. The criteria for these groupings were the fasting blood sugar level, the height of the hyperglycemia, its duration and the time required for the blood sugar to return to its starving level. On this basis we have considered as mild diabetics (Table 1) those patients whose starving blood sugar was normal but rose above the accepted value after the ingestion of 100 gm. of dextrose and yet showed a distinct fall at the third hour. The moderately severe group (Table 2) includes patients with a fasting blood sugar below 150 mg., a marked hyperglycemia following 100 gm. of dextrose and the persistence of this rise at the third hour of the curve. The severe group (Table 3) includes those patients in whom the starving blood sugar was above 160 mg. and in whom the hyperglycemia was maintained for the entire 5-hour period.

In the group of normals (Table 4) the results are similar to the normal curves reported by Gray[1] in his analysis of blood sugar standards. The blood sugars at the fourth and fifth hours showed a drop in 4 cases and a slight rise in 2. Several levulose tolerance curves had been done on Case 1, and the character of the curve corresponds to those of individuals who have been used to carbohydrate stimulation. The curve of Case 26, with renal glycosuria, is a normal curve, with the exception that the starving sugar level is lower than normal.

TABLE 4.—NORMAL.

Case No.	Blood sugar, mg. per 100 cc. Number of hours after taking 100 gm. glucose.							Greatest rise in mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.
	Starv.	0.5	1.	2.	3.	4.	5.			
1*	100.0	91	86	77	73	57.0	64			
2	75.0	160	125	93	79	61.0	55	85	1	
3	76.0	121	133	133	44	57.0	66	57	2	0.65
4	84.0	156	113	80	71	82.0	92	72	1	
5	100.0	122	156	121	103	86.9	80	56	2	
26†	68.3	123	152	110	90	75.5	67	84	1	0.60

* This patient had had several levulose tolerance curves done during the 10 days preceding this dextrose curve. The character of this curve corresponds to those of patients who have been used to stimulation of their carbohydrate mechanism.

† This patient is the renal [illegible]

Discussion. In correlating the clinical severity of the diabetes with the type of the glucose tolerance curve exhibited by each group, we found that in the mild clinical group 1 case (Case 25) had a curve of the moderately severe type. In spite of the character of the blood sugar curve in this patient, it is interesting to note that he continues to remain sugar free on an adequate diet with a carbohydrate content of 142 gm. In the moderate severe clinical group; 2 cases (Cases 17 and 18) showed curves characteristic of the severe type. In spite of the prolonged hyperglycemia these 2 patients do not require insulin and remain sugar free on diets containing 160 gm. and 142 gm. of carbohydrate respectively. In the severe group Case 17 is the least severe case, showing the lowest blood sugar at the fifth hour and one of the smallest rises in milligrams of blood sugar. The severe group as selected clinically all showed the prolonged severe type of tolerance curve.

The discrepancy between the clinical severity of the disease and the response to 100 gm. of dextrose followed for the 5-hour period requires explanation. It seemed to us that the patients who were exceptions to their clinical grouping probably have a higher renal threshold for sugar which is not exceeded by their ordinary divided carbohydrate intake. This is substantiated in Cases 17 and 18 by the fact that less sugar was spilled in the urine during the experimental period than in the other cases in the severe group. Another fact that must be considered is the rate of absorption. Case 17 is a cardiac patient with auricular fibrillation and, although the patient was fully digitalized and had no signs of congestion at the time the curve was done, the rate of absorption might have been lowered.

In analyzing the blood sugar curves in the mild group it seems to us significant that the 1 patient (Case 9) in whom the blood sugar

had not returned to the starving level by the fourth hour is the patient who continues to require a definitely restricted carbohydrate

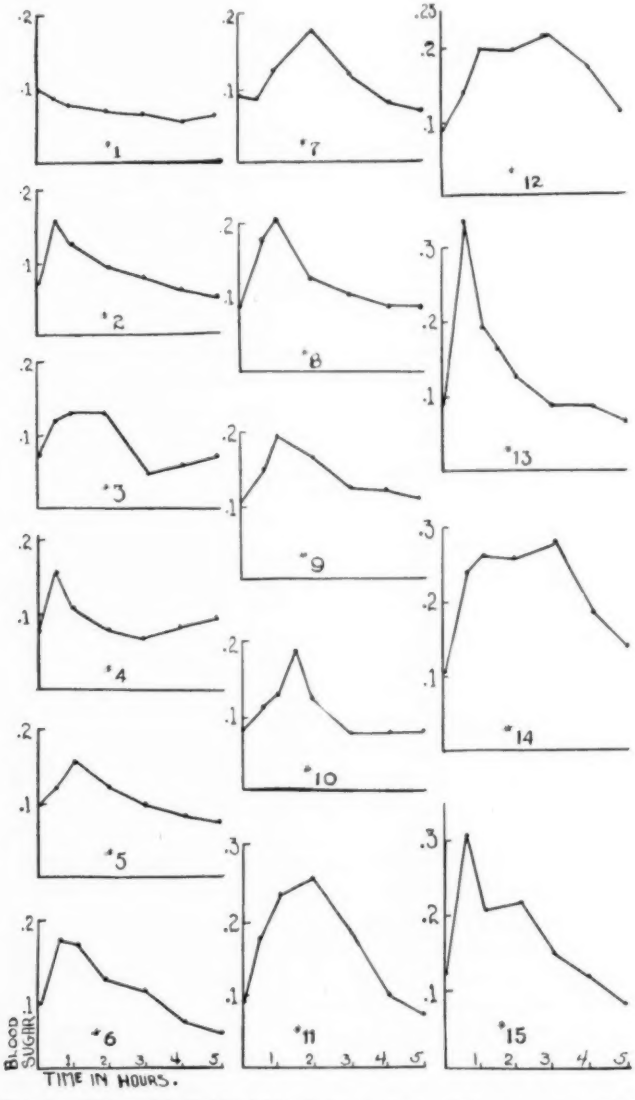

FIG. 1.—Chart of individual blood sugar curves of the cases reported.

diet. Three of the patients (Cases 6, 7 and 13) reached at the fifth hour a blood sugar level lower than their starving level. This may be explained on the hypothesis of MacLean and De Wesselow,[6]

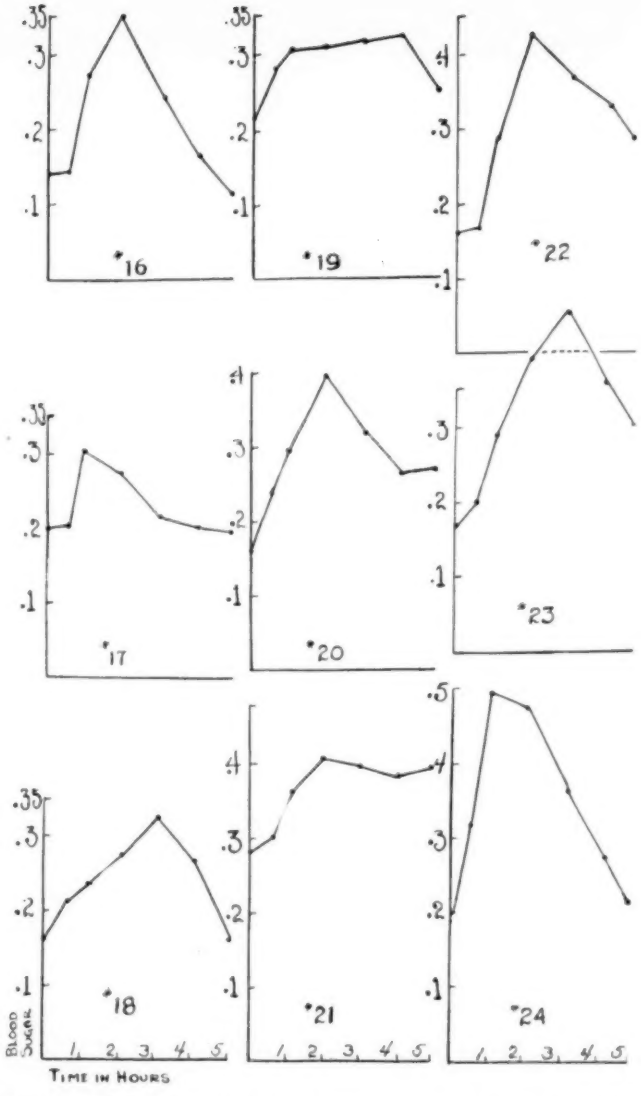

FIG. 2.—Chart of individual blood sugar curves of the cases reported.

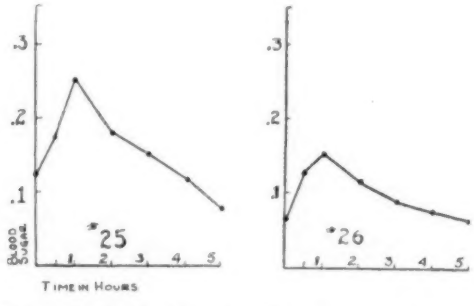

FIG. 3.—Chart of individual blood sugar curves of the cases reported.

supported by the observations of Foster,[12] that following the ingestion of glucose there is an overstimulation of the glycogen-forming function of the liver. Apparently in the mild diabetic this response is not abolished, whereas in the severe diabetic glycogen synthesis does not occur to any appreciable extent and hyperglycemia continues unchecked.

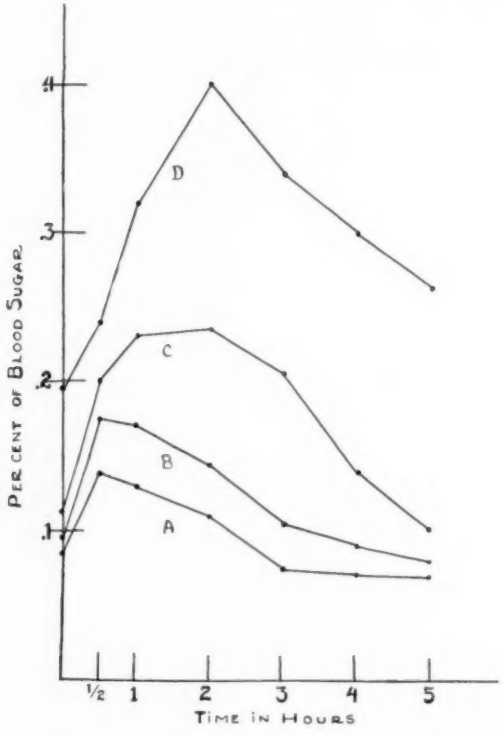

FIG. 4.—Average of the five-hour curves in the four groups studied: *A*, average of normal group; *B*, average of the mild diabetics; *C*, average of the moderately severe group; *E*, average of the severe group.

In the moderately severe group 3 cases (Cases 11, 15 and 25), with blood sugars at the third hour of 186 mg., 153 mg. and 150 mg., reached a normal blood sugar at the fifth hour. The other 3 cases all had blood sugars above 200 mg. at the third hour and at the fifth hour were still above 120 mg. Apparently the patient whose blood sugar is above 200 mg. at the third hour will not reach the fifth hour with a blood sugar below or equal to his starving level. This group also bears out the observation of Ohler,[10] that the fasting blood sugar gives only partial and often misleading information. In all but 1 of these patients the fasting sugar was below

148 mg. and, although the total rise in milligrams of blood sugar was greater in the patient with the higher fasting level, the hyperglycemia was not maintained for any longer period of time.

MacLean and De Wesselow[6] studied the blood-sugar curve in a moderately severe diabetic over a five-hour period and found the initial blood-sugar level was not regained until the end of that time. This inability on the part of the diabetic patient to regain his starving blood sugar level seems to us to be of real clinical significance. The amount of carbohydrate at any one time should not so overload

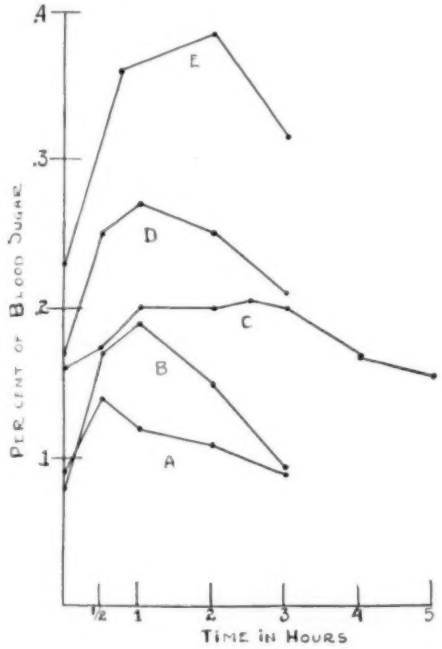

FIG. 5.—Three-hour blood sugar curves plotted from the results of other investigators. *A*, average of normals from Gray;[1] *B*, average of diabetics with fasting blood sugars below 120 mg. from Gray;[1] *C*, five-hour curve reported by MacLean and De Wesselow;[6] *D*, average of diabetics with fasting blood sugars above 120 mg. from Gray;[1] *E*, average of Wishnofsky's 17 cases.[4]

the carbohydrate mechanism that the patient will reach his next feeding with an abnormal blood sugar level. The state of the blood sugar can readily be ascertained by doing a blood sugar before the next meal or 4 hours after the previous meal. This seems to us more important than a starving blood sugar.

In both the moderately severe and the severe group the blood sugar level at the third hour is distinctly abnormal. In the former group this level is lower than in the severe group. As mentioned previously, the lowest blood sugar curve in the severe group was

that of Case 17, who was classified as moderately severe clinically. The important fact in these two groups is whether or not the hyperglycemia is maintained. Can one assume that a blood sugar at the third hour below 275 mg., the highest in the moderately severe group, will fall to a reasonable level at the fifth hour? It seems to us that this question is best answered by an estimation of the blood sugar content at a later hour. The clinically moderately severe diabetic is the patient who manages to control his hyperglycemia by the fourth or fifth hour, regardless of its rise.

In the present study, with three exceptions, the classification, based on the clinical course of the diabetes, was confirmed by the glucose tolerance curves. In view of this, it would seem unnecessary to resort to a tolerance test for the purpose of estimating the severity of the disease, provided there is sufficient time to observe the patient under proper conditions. If this is not possible, and a tolerance test is used to establish the severity of the diabetes, we feel that the height of the blood sugar at the fifth hour gives more definite information on this point than the 3-hour test.

All the patients were seen in the clinic 3 to 5 days after the tolerance curves had been done. All were sugar free and had suffered no untoward effects as a result of the test. We have found no evidence of permanent or even transient impairment of the carbohydrate mechanism in any of the patients studied. Allen,[13] Ohler[10] and several other investigators warn of the disastrous effect of a large dose of glucose; we did not have this experience.

Summary. 1. The blood sugar curve following the ingestion of 100 gm. of dextrose was studied for a 5-hour period instead of the customary 3 hours in normal individuals and in mild, moderate and severe diabetics.

2. In the normal group the blood sugar reaches its height in from 0.5 to 1 hour. The blood sugar returned to a normal level at the second or third hour.

3. In the group of mild diabetics the return of the blood sugar to its starving level was at the third or fourth hour. The greatest hyperglycemia was at the first or second hour.

4. In the moderately severe group the return of the blood sugar to its starving level was delayed to the fourth or fifth hour. The greatest hyperglycemia occurred at variable periods.

5. In the severe group the blood sugar was markedly elevated for the entire 5-hour period.

6. There is evidence presented that a starving blood sugar level of over 160 mg. suggests that the patient will not return to this level within a period of 5 hours following the ingestion of 100 gm. of dextrose.

Conclusions. 1. It is suggested that the blood sugar level taken 4 hours after a meal is a better index of the severity of the diabetes than the starving blood sugar.

2. The severity of the diabetes as classified by clinical criteria was supported in all but 3 cases by the glucose tolerance test.

3. The 5-hour test is found to give more valuable information in many cases than the 3-hour test.

BIBLIOGRAPHY.

1. Gray, H.: Blood Sugar Standards, Normal and Diabetic, Arch. Int. Med., 1923, **31**, 241.

2. John, H. J.: Glucose Tolerance Test and Its Value in Diagnosis, J. Metab. Res., 1922, **1**, 497.

3. Rowe, A. H., and Rogers, H.: Carbohydrate Tolerance in Normal Persons and in Nondiabetic Patients, Arch. Int. Med., 1926, **39**, 330.

4. Wishnofsky, M.: The Dextrose Tolerance Test: Its Use in the Determination of the Severity of Diabetes Mellitus, Arch. Int. Med., 1928, **42**, 443.

5. Mosenthal, H.: The Interpretation of Sugar Tolerance Tests, Med. Clin. North America, 1925, **9**, 549.

6. MacLean, H., and De Wesselow, O. L. V.: The Estimation of Sugar Tolerance, Quart. J. Med., 1920–1921, **14**, 103.

7. Rabinowitch, I. M.: Simultaneous Respiratory Exchange and Blood Sugar Time Curves Obtained in Diabetic and Nondiabetic Individuals Following Ingestion of Glucose, J. Clin. Invest., 1925–1926, **2**, 143.

8. Sweeney, J. S.: Dietary Factors That Influence the Dextrose Tolerance Test, Arch. Int. Med., 1927, **40**, 818.

9. Hale-White, R., and Payne, W.: The Diagnostic Value of Dextrose Tolerance Curves, Quart. J. Med., 1926–1927, **20**, 457.

10. Ohler, W. R.: Lessons to be Learned from Repeated Glucose Tolerance Tests, Med. Clin. North America, 1922, **5**, 1465.

11. Folin, O., and Wu, H.: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem., 1920, **40**, 367.

12. Foster, G. L.: Carbohydrate Metabolism: Interpretations of Blood Sugar Phenomena Following Ingestion of Glucose, J. Biol. Chem., 1923, **55**, 203.

13. Allen, F.: Production and Control of Diabetes in the Dog: Effects of Carbohydrate Diets, J. Exp. Med., 1920, **31**, 381.

PSEUDONEOPLASTIC LUETIC GRANULOMATA.

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It is a commonplace of medical practice that syphilis in the protean manifestations of its tertiary stage may resemble almost any disease form. In bones and in other organs, where isolated luetic lesions have been more commonly reported, both the clinician and the roentgenologist have been on the alert especially for those

forms which simulate tumors. In or about muscles, however, syphilis appears to have a particular tendency to the formation of tumor-like growths. It is doubtless to the relatively rare occurrence of this form of the disease that the errors in diagnosis are to be attributed. Where these tumefactions are localized simulating benign growths the dilemma may not be as difficult or important to resolve as where they are infiltrating in nature. In these latter cases diagnostic misinterpretations may sometimes involve serious consequences as is shown by reference to the literature. In Chastenet de Gery's[1] case a recurring tumor and a mistaken biopsy specimen almost resulted in disarticulation at the hip; Deniker[2] reported a case in which the biceps cruris was resected; Köhler[3] described another in which he erroneously removed the muscles of one-half of the abdominal wall, while Planson[4] performed a myomectomy of the latissimus dorsi.

The occurrence of 2 such cases on our service within a relatively short time aroused our interest in the subject, and search of the hospital records unearthed 3 other somewhat similar cases occurring either in the muscle or fascia about the knee. They are presented in the hope that they may direct attention to this manifestation of lues and possibly save the patient an unwarranted operation and the surgeon unnecessary chagrin. Roughly, they may be divided into two main groups—one in which a discrete, apparently benign tumor formation was observed and a second in which a more diffuse invasion of the muscle led to the suspicion of a malignant neoplasm.

In the first group we present 2 cases:

Case Reports. Case 1.—M. F., female, colored, aged 48 years, was seen in the Outpatient Department of the Hospital for Joint Diseases in 1921, complaining of a swelling of the left prepatellar region. The prepatellar bursa was excised and the patient made an uneventful recovery. In 1925 the patient returned to the dispensary, stating that a small tumor had developed slightly lateral to the site of the previous operation. This was painless, but was slowly growing in size. This mass was diagnosed as a benign tumor and was excised. The pathologic report was: "Gross: Specimen consists of a small nodule, measuring 1 cm. in its greatest diameter. This is a rubber-firm tissue; on section it is white. Microscopic (Fig. 1) sections show a fibrous nodule with numerous areas of perivascular round-cell infiltration; plasma cells and an occasional giant cell are to be seen. Diagnosis: gumma." The patient disappeared from the dispensary until March, 1928, when she again returned complaining of pain on walking. Careful examination disclosed a small hard nodule on the outer side of the knee joint with the knee in flexion. Roentgen ray of the knee showed a chronic productive osteoarthritis. When advised to take antiluetic treatment the patient demurred, and has not been seen since.

The next case is almost the exact parallel of the above case, though it appeared to arise beneath rather than in the muscle.

Case 2.—J. P., male, colored, aged 30 years, was admitted to the hospital on November 10, 1930, complaining of pain and stiffness in the left knee.

The present illness began 6 months prior to admission, with slight pain in the left knee, occurring chiefly at night, and awaking him from sleep. The pain disappeared upon activity. About 3 months after onset he noticed a mass above and to the outside of the knee cap, which had gradually increased in size. The pain has increased in severity, and in the past month there has been some interference with motion of the knee upon arising in the morning. The patient was born in Porto Rico. He remembers no serious illnesses. His tonsils were removed 13 years ago. No history of venereal diseases could be elicited. The patient has been married 20 years and has a wife and 1 child living and well. There was no history of miscarriages.

Physical examination revealed a well-nourished, well-developed adult, with no significant physical findings, except for the local orthopedic condition. In the suprapatellar region, just beneath the vastus externus, there was a globular mass, about 4 cm. in diameter, of resilient consistency, not attached to the skin. The tumor mass was deeply situated and seemed to be attached by a fasciculus to the upper outer border of the patella, at which point there was some tenderness. The motions of the knee were normal. No fluid was present in the knee joint. Laboratory examinations revealed the following: Wassermann, 2+, with cholesterinized antigen. Blood count: White blood cells, 5400; polymorphonuclears, 34 per cent; lymphocytes, 55 per cent; eosinophils, 9 per cent; monocytes, 2 per cent; hemoglobin, 80 per cent. The roentgenologist reported "hypertrophic arthritis, with no pronounced bone atrophy." A tentative diagnosis of soft tissue tumor about the knee, fibroma or lipoma was made and operation advised.

At operation, on November 13, 1930, a 4-inch incision was made directly over the tumor mass in the lower external aspect of the thigh, exposing a tumor mass about the size of an egg, superficially covered with fatty tissue, of fibrous consistency and apparently situated beneath the muscles. The tumor extended distally to the patella, to which it was firmly attached and merged with the capsule of the joint. The mass was not incapsulated. The growth was dissected out *en masse*. At several points it was necessary to remove small portions of the suprapatellar pouch, exposing the joint cavity which showed an injected hypertrophied synovial membrane. The wounds in the joint capsule were repaired with chromic sutures, and the wound was closed in layers. Union occurred by primary intention. The tumor appeared completely benign and a postoperative diagnosis of fibroma was made. However, to everyone's great surprise, the pathologic report by Dr. Jaffee read as follows: "Gross: Specimen consists of a very firm piece of fibrous tissue, measuring 4 by 3 by 2 cm. Microscopic section (Fig. 2) reveals rather dense fibrous tissue, which shows evidence of a very extensive chronic granuloma. This is manifested by very dense lymphoid infiltration. In other places the formation of tuberculoma-like lesions, with numerous giant cells, is present. Some of the larger blood-vessels are surrounded by giant cells. These tubercle-like lesions show in places fusion into conglomerate masses. No caseation is present. Diagnosis: gumma." The patient was discharged with the wound fully healed, on November 23, 1930, and is now receiving antiluetic treatment in the Outpatient Department.

In the second group, in which the diagnosis of a malignant growth was made pre-operatively, we present 3 cases.

CASE 3.—W. G., male, white, aged 36 years, was seen at the clinic at the Hospital for Joint Diseases on November 24, 1930, complaining of a

large lump on the outer aspect of his right knee for the past 5 months. This mass was painless, very hard and had been gradually growing in size. There had never been symptoms of acute inflammation nor interference with motion of the knee. The patient walked without a limp. He observed that in the nature of his work at a machine, this mass had been continually exposed to slight blows against the machine. The patient was married. His wife and 2 children were living and well, but there was a history of several miscarriages in the family. The patient absolutely denied affliction either with lues or gonorrhea. A Wassermann performed on the outside was reported as completely negative.

Apart from the local condition, there were no positive physical findings. Over the anterolateral aspect of the right knee joint, extending from the lateral border of the patella to beyond the posterior border of the fibula, and from about the level of the tibial tubercle to the upper border of the outer condyle, there was a firm, somewhat lobulated, elastic, nontender mass, about 3 inches in its longest diameter, apparently fixed to the underlying structures and to a lesser degree, to the skin. There was no interference with the gait of the patient, no limitation of motion in the knee joint and no fluid, crepitus or abnormal mobility in the knee joint. The inguinal glands were not enlarged. The Roentgen ray was reported as showing no evidence of bone involvement, and a diagnosis of "pretibial soft tissue swelling" was made. The patient was admitted to the hospital on December 3, with a pre-operative diagnosis of tumor of the right knee joint capsule.

On December 4 a 4-inch incision over the tumor mass disclosed a grayish-red elastic, irregular tumor mass apparently attached to the lateral aspect of the knee joint, but not involving the joint itself. With some difficulty the mass was dissected away from the skin, the biceps tendon and the peroneal nerve which it surrounded. The upper portion of the tibialis anticus muscle was apparently involved in the growth and was dissected with the tumor mass. The wound was closed in layers.

Upon sectioning the tumor after its removal, we realized that we were dealing with a tumor mass that was not characteristically malignant, and which still did not belong to the group of typically benign tumors. A check-up Wassermann reported several days later first aroused our suspicion that we were dealing with one of the manifestations of syphilis. This suspicion was somewhat confirmed by the pathologic report of Dr. Jaffee, which is herewith appended: "Gross: Specimen consists of a flat piece of tissue measuring 8 by 5 by 1 cm. in thickness. Several sections taken showed a fibrous tissue. Joint capsule was also taken. Microscopic (Fig. 3): Sections show a thickened connective tissue, very densely infiltrated with lymphocytes, showing also large collections of lymphocytes about some of the bloodvessels, and in other areas showing epithelioid proliferations resembling but not typical of tuberculosis. Scattered through the sections there are some giant cells, one of the sections having a fairly large number. The same type of lesion is found in the capsule of the joint. The lesion is a granuloma. All tumors may be excluded. Tuberculosis, I believe, may also be excluded. The possibilities are that the lesion is syphilitic, though typical gummata are not observed. Diagnosis: Luetic (?) granuloma about the knee."

The record of the following case has been very graciously put at our disposal by Dr. Philip M. Graussman, surgical director at the hospital.

CASE 4.—M. K., male, aged 29 years, was seen in the Outpatient Department on October 21, 1928, complaining of a tumor in the lower portion of

FIG. 1.—Marked sclerosis, round-cell nodules and occasional giant cells. (× 100.)

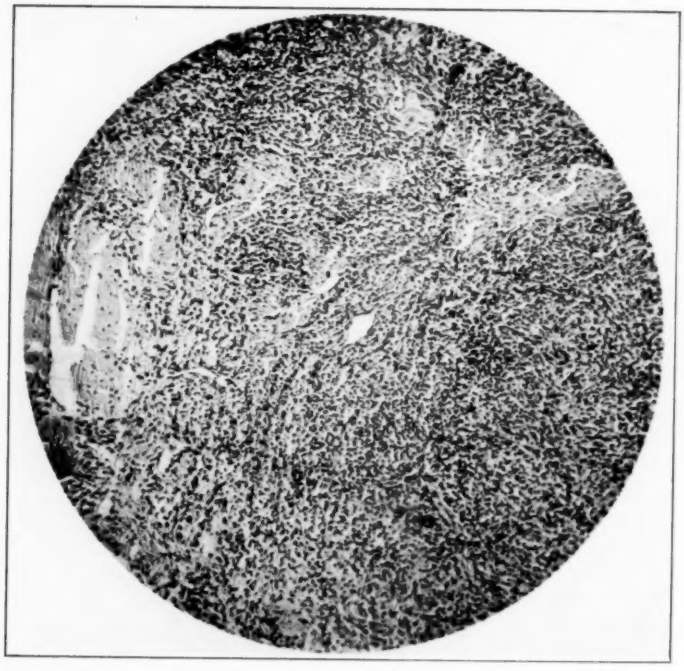

FIG. 2.—Dense lymphoid infiltration. (× 110.)

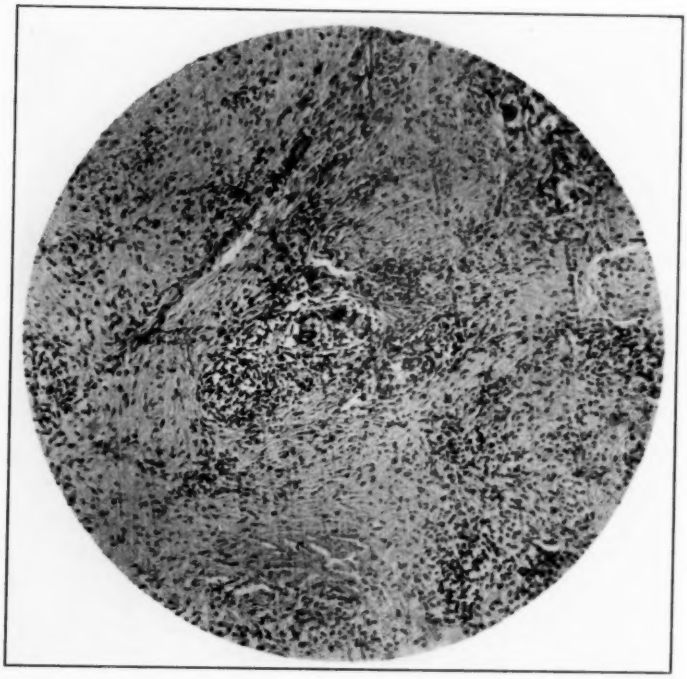

FIG. 3.—Sclerosis. Perivascular infiltration; epithelioid proliferation. (× 110.)

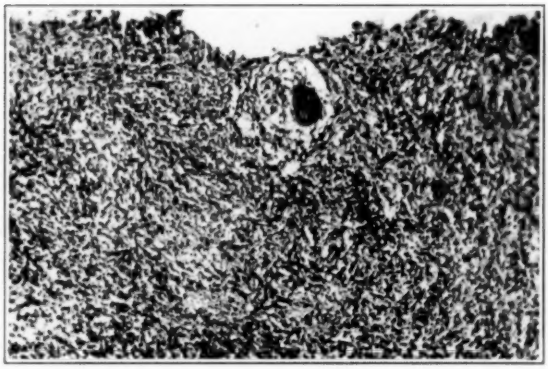

FIG. 4.—Edge of necrotic area. Epithelioid proliferation; occasional giant cell; lymphoid infiltration; sclerosis not as marked as in other specimens. (× 120.)

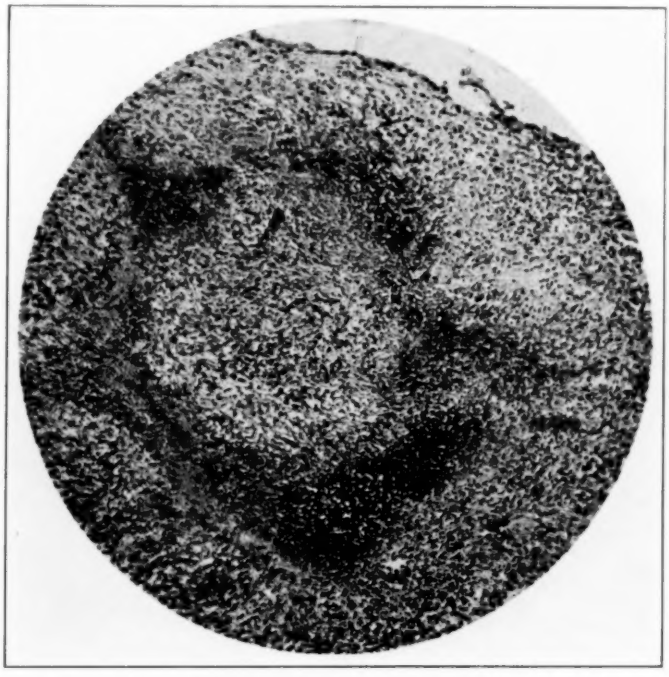

FIG. 5.—Gumma formation at edge of necrotic mass. (× 100.)

the left thigh. This tumor was somewhat nodular in places and somewhat fluctuating in other places. The patient gave a history of chancre 14 years ago. He stated that he had received vigorous antiluetic treatment and had been told he was cured. All other manifestations of the disease were denied. Six months ago, without any other history of trauma, a mass which had been gradually growing in size was noticed on the inner aspect of the left thigh. The mass was not painful, appeared to be somewhat adherent to the skin on the inner aspect of the knee joint and its lower pole and was about the size of a large lemon. Beyond this nothing was found. In view of the history of lues, the patient was given rather intensive antiluetic treatment without any effects whatsoever. On November 1, 1928, the patient was admitted to the hospital with a diagnosis of neoplasm of the thigh. The Wassermann was 4+. The leukocyte count showed 12,000, with 80 per cent polymorphonuclears. On November 13, 1928, this patient was operated upon, and a tumor was found adherent to the muscles of the underlying structures. This was completely removed and the pathologist, Dr. Jaffee, reported: "Gross: Specimen consists of a tumor mass, measuring 8 by 5 by 4 cm., with several smaller pieces. This tumor mass has attached to it a piece of very firm aponeurosis. Part of it is encapsulated. On opening it, it showed a soft greenish-gray necrotic mass. Microscopic (Fig. 4): For the most part, the mass consists of complete necrotic tissue. It is surrounded by a very vascular granulation tissue with numerous lymphocytes and also areas in which there is an epithelioid proliferation and some giant cells. Diagnosis: gumma." The patient made an uneventful recovery and has since been lost sight of.

This last case is interesting because it was only after careful reëxamination of the slides in the light of the clinical history that the pathologist was enabled to ultimately arrive at a diagnosis.

Case 5.—J. C., male, aged 36 years, colored, born in United States, was seen in the Outpatient Department of the Hospital in April, 1929, complaining of swelling of the left knee. He stated that on January, 1929, he had fallen and injured his left knee. The knee became swollen and slightly painful. The pain was somewhat intermittent in character, and some time later the patient noticed the development of a lump on the inner aspect of the left knee gradually growing in size. There never had been any interference with motion.

The patient denied chancre or other secondary luetic manifestations. In 1919 a lump was excised from the left groin. This lump was painful and attributed by the patient to an injury. In 1923 he was struck on the left knee by an automobile crank-handle; he made a slow recovery from this injury, but since then the knee has been painful in bad weather. In 1924 he was treated in the Harlem Hospital for gonorrhea and lues.

When first seen, in 1929, there was a freely movable swelling, the size of a large lemon, connected with the vastus internus muscle on the left knee. There was a moderate effusion into the knee joint, but no limitation of motion whatsoever in any direction. The tumor mass was painless, somewhat nodular in places and somewhat elastic in other places, and seemed to infiltrate the muscle. The pupils reacted to light and accommodation somewhat sluggishly. A slight systolic murmur was heard at the apex and was transmitted to the axilla only after exercise. All other physical findings were negative. In spite of the Wassermann test, which was reported 4+, it was clinically felt that this tumor mass presented too much the appearance of a malignant neoplasm to warrant delay. The patient was admitted to the hospital with a diagnosis of malignant tumor of the thigh.

On April 18, 1929, the tumor mass was exposed through an 8-inch incision made along the inner aspect of the thigh. The fascia over the mass was adherent to it and to the quadriceps tendon. The mass was found to consist of several smaller nodular masses occupying the whole thickness of the quadriceps muscle and tendon, and the vastus internus muscle. A large area of the quadriceps tendon and muscle and of the vastus internus muscle were excised to remove the tumor mass in one piece. In doing this, the joint was opened. The wound was closed in the usual manner, and the patient made an uneventful convalescence. The pathologist reported: "Gross: Specimen consists of a large piece of muscle and some fascia adherent to it. The muscles showed some areas of necrosis, some areas of marked interstitial myositis and other of yellowish caseation. Microscopic section (Fig. 5) showed numerous areas of necrosis and granulation tissue reaction. Evidences of an interstitial myositis. There are no evidences of gummata or syphilitic lesion. Diagnosis: abscesses of muscle with interstitial myositis." Following an uneventful convalescence, the patient was discharged from the Outpatient Department, where vigorous antiluetic treatment was resumed.

The history of lues with a positive Wassermann in the presence of an infiltrating tumor of muscle which on section showed the characteristic yellowish caseating areas of necrosis led us to believe that the myositis above reported was luetic in nature; we requested a revision of the slides. With the additional clinical information which we were able to supply, Dr. Jaffee restudied the slides, and after careful search found what he considered to be small gummata. The report was thereupon amended in the following sense: "Reëxamination of the slides shows at the periphery of the necrotic mass gumma-like formations. In view of the history and examination of the slides, believe the lesion is probably syphilitic."

Pathologically, tertiary muscular syphilis has been described as occurring in two main forms, and a third form which is a combination of the former two. The first type, the interstitial myositis, presents the picture usually found in other diffuse myositides and is characterized by vascular dilatation, infiltration of round and plasma cells, atrophy of the muscle fibers and increase of the interstitial connective tissue which leads subsequently to a diffuse sclerosis. This type, which is most frequently found in the sphincter ani, the masseter and biceps, is not of the tumor-forming variety, and does not enter into our consideration. It is the latter two, the gummatous and the sclerogummatous types, which present tumefaction and which may be said grossly to correspond to the two clinical types previously mentioned. The gummatous type, under which Cases 1 and 2 may be classed, is by far the commoner and occurs most frequently in the sternomastoid and in the crural muscles. It usually appears as a single lesion, but may be multiple and even symmetrical in its distribution. It is usually found in the belly of the muscle at the origin of the tendon and varies greatly in size. On section, it presents a whitish, reddish or yellowish appearance in which caseating areas may be seen. These necrotic centers increase in size until ultimately the whole mass may become completely necrotic. Microscopically, the muscle fibers are found separated and atrophied. In the connective tissue between the muscle bundles lie nodules of round and plasma cells, which may

or may not contain giant cells of the Langhan variety. As these nodules increase in size, their centers become necrotic and by their confluence present the picture of a tumor mass, necrotic in the center which is so characteristic of the larger gummata. In the combined or the sclerogummatous form of the disease both of these pathologic pictures are present in varying degrees. It appears, however, that the single caseating gumma is replaced by the appearance in the midst of a hard, infiltrating pseudoneoplastic mass of numerous miliary gummata of which Köhler says: "Such caseating foci situated in apparently sarcomatous masses can be considered as almost pathognomonic of syphilis." This is the type of lesion which was found in our Cases 3, 4 and 5.

Though Köhler considers the gross appearance so characteristic as to be pathognomonic, the differentiation from tuberculosis or other chronic infections may at times present the utmost difficulty. Indeed, even microscopically, the diagnosis may occasionally be impossible. Practically all of the pathologists who have discussed the subject agree that apart from the actual demonstration of the specific organism in the tissues, the differentiation between these miliary gummata and tubercles can at times not be made. In such cases the ultimate decision must rest with the clinician.

Because of the fact that the sclerogummatous forms may so closely resemble malignant neoplasms the clinical diagnosis is, of course, of vital moment in determining both the prognosis and the method of treatment. The history of exposure to luetic infection or the presence of a positive Wassermann reaction either in the blood or spinal fluid, associated with the appearance of a tumor in the muscles should always suggest the possibility of a sclerogummatous type of muscular syphilis. In such cases the reaction of the tumor mass to antiluetic treatment will be of determining moment. In fact, Nelaton remarked: "Every muscle tumor must first be treated with antiluetic measures." The disappearance of a large, apparently malignant muscular tumor under antiluetic treatment will determine its origin.

Summary. Five cases are presented in which operation was undertaken for tumors in or about muscles which subsequently proved to be luetic in nature. Attention is called to the fact that, both clinically and pathologically, the differential diagnosis between the relatively benign pseudoneoplastic luetic masses and true malignant tumors may be difficult. In all such cases operation should be deferred until careful tests, including the reaction to therapy, can be made to rule out the possibility of lues.

REFERENCES.

1. Chastenet de Gery: La méd., 1928, **9**, 99.
2. Deniker, M.: Bull. et mém. Soc. nat. d. chir., 1927, **53**, 1434.
3. Köhler, R.: Berl. klin. Wchnschr., 1892, **29**, 162.
4. Planson, M. V.: Bull. et mém. Soc. d. chir., 1929, **21**, 564.

REVIEWS.

FOOD ALLERGY. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco. Pp. 442. Philadelphia: Lea & Febiger, 1931. Price, $5.00.

THE author has written comprehensively on the subject of food allergy. His most important contribution is the recommendation of elimination diets, which he devised. Their importance is appreciated when it is realized that 60 per cent of all patients with food sensitivity have negative skin reactions. Meticulous care is shown in the arrangement of these diets and in the directions for preparing them.

Not all clinicians and allergists can agree with Dr. Rowe in his statement that "Allergy, and as a part of it, food allergy, is probably next to infection the most common and important single etiologic agent in human symptomatology." Not all of us can accept as allergic or as possibly allergic all diseases of the gastrointestinal tract without demonstrable organic pathology; mucous collitis, proctitis, pruritus ani, gastrointestinal bleeding, tic douloureaux, spasmodic croup, psoriasis, Ménières syndrome, dysmenorrhea, arthritis, arthralgia and epilepsy. Despite our skepticism, we envy anybody who can, by any method of treatment, obtain good or excellent results in 94 per cent of 400 patients with allergic disease. S. L.

INTESTINAL TUBERCULOSIS. ITS IMPORTANCE, DIAGNOSIS AND TREATMENT. By LAWRASON BROWN, M.D., Consultant to the Trudeau Sanitarium, and HORACE L. SAMPSON, Roentgenographer of the Trudeau Sanitarium, Saranac Lake, New York. Pp. 376; 122 engravings and 2 colored plates. Second Edition. Philadelphia: Lea & Febiger, 1930. Price, $4.75.

A NEW edition, enlarged and revised, of a book which was the first authoritative presentation of the subject. This monograph gives an unusually thorough and complete discussion, with numerous case reports, many excellent illustrative roentgenograms and a full survey of the literature: it is truly the first and the last word on intestinal tuberculosis. R. K.

HEALTH AT THE GATEWAY. By E. W. HOPE, O.B.E., M.D., D.Sc., Professor of Public Health, University of Liverpool; formerly Medical Officer of Health, City and Port of Liverpool. Pp. 213; illustrated. London: Cambridge University Press, 1931.

THE happily chosen title of this volume can scarcely fail to arouse one's curiosity as to its subject matter. Between its covers is packed a wealth of information concerning all of the major and most of the minor problems with which public health is concerned in the large seaport city of Liverpool. Unlike the general run of works dealing with public health, this one presents not only the experiences of the author during a long lifetime as health officer but also presents a scholarly review and interpretation of the various experiences of past generations upon which the modern development of public health measures has been based. It is impossible to pick out any single items for special comment, but mention should perhaps be made of the chapter dealing with the great plagues and pestilences of the past and of that concerned with maternal, infant and childhood morbidity and mortality. Despite the inclusion of much statistical material and of much reference to the political aspects of the problem, of public health, the author has succeeded in presenting the entire matter in the form of a most readable and altogether dramatic story which should appeal alike to the layman, the practitioner of medicine and to the public health officer. C. E.

DIE CHIRURGIE DES KROPFES. By DR. KARL URBAN. Pp. 85; 51 illustrations. Leipzig and Wien.: Fraz Deuticke, 1931. Price, M. 6.80; geb. M. 8.80.

A MONOGRAPH based on the personal observations of the author over a period of 30 years during which time he performed 4250 operations for goiter, with a mortality of only 0.9 per cent, the paper covers the entire range of the surgical treatment of disturbances of the thyroid in a clear and frank manner. The author is convinced that the best results are obtained from a subtotal resection of the gland ("enucleationreseckion") taking care to leave behind a broad but thin capsule. He uses local anesthesia and nonabsorbable sutures. The former is preferred as he can keep better posted as to the condition of the recurrent laryngeal nerves and does away with the danger of asphyxiation in the large goiters. Chronic thyroiditis (Riedel-Struma) is discussed and a case reported in which the combination of Roentgen ray therapy and surgery was effectual. In discussing the prophylaxis of goiter he warns against the indiscriminate use of iodin and emphasizes the dangers of such administration. He finds no decrease in the incidence of goiter in Austria. Injuries of the parathyroids should not occur if his technique of

leaving behind a broad posterior capsule is followed. A pre-operative milk and vegetable diet also makes the occurrence of tetany less likely. The administration of parathyroid hormone is preferable to transplantation of parathyroids in cases of tetany. Injuries to the recurrent laryngeal nerve are more frequent than statistics indicate (10 per cent in the author's series), as a large proportion of them are only discovered by routine pre-operative and postoperative laryngoscopic examination. In the treatment of cachexia strumipriva he believes that transplantation of thyroid tissue is only of temporary value until the patient's thyroid remnants can resume their function. From a study of 3000 transplantations done in feeble-minded children he found that the transplant never lasted longer than 6 months and were usually resorbed sooner.

He discusses briefly the subject of benign metastasizing thyroid adenoma. The only one that he has observed was in a woman, aged 47 years, who developed tumors in her left femur and left clavicle 5 years after the removal of a cystic goiter. Surgery and Roentgen ray were effectual.

Three hundred cases of Basedow's disease have been treated by the author with a mortality of only 2.4 per cent. He states that the European form differs from that seen in America, being almost entirely the parenchymatous type, whereas ours are mainly the adenomatous type. While he does not feel that the European type can be safely treated with iodin, he refers to the brilliant results obtained in America from its use. He employs physical therapy, diet, fresh air and Roentgen ray treatment to a far greater degree than used in this country. As in the operation for simple goiter, he advocates a subtotal resection leaving a broad thin posterior capsule, preferring to remove too little tissue than too much and rather performing a secondary operation than leaving the patient with myxedema. He has only had to perform two such operations.

R. M., Jr.

Nervous and Mental Disease Monograph, Series No. 53. Brain and Personality. By Paul Schilder, M.D., Ph.D., Research Professor of Psychiatry, New York University. Pp. 136. New York and Washington: Nervous and Mental Disease Publishing Company, 1931. Price, $3.00.

This monograph, by a distinguished research worker of the psychoanalytic school, embraces two series of lectures: The Psychological Aspect of Cerebral Neuropathology and the Relation Between the Personality and Motility of Schizophrenics.

In the section on Encephalitis much important matter concerning the centers regulating sleep is correlated.

The "Id" is represented in the parts of the brain which are philo-

genetically older—around the cerebral ventriculi—and herein chiefly lies the disturbance in schizophrenics; the "Ego" is beyond this and is concerned with the confusional states; in the cortical layer are found the disturbances of agnosia, aphasia and dementia.

More formal treatment of the subject-matter would aid the reader not thoroughly conversant with psychoanalysis and, where possible a definite case report would be better than so much patchwork mixing of a case in the text.

There is a fair bibliography, but the index, said to be on page 137, is wholly absent. N. Y.

THE THEORY OF OBSTETRICS. By M. C. DE GARIS, M.D. Pp. 272. New York: William Wood & Co., 1931. Price, $5.00.

THE author has developed some new individual and interesting theories regarding certain obstetrical problems. His theory is a personal one and he supports it by a certain method of reasoning which may not appeal to all obstetricians. However, his intriguing speculation is stimulating and many of his subjects might well be considered. The author feels that uterine inertia is a central and fundamental problem of obstetrics and feels that underlying inertia uteri are albuminuric and pyelitic manifestations and, just as largely, hidden dental sepsis. He makes a plea for research and for a more careful individual analysis of obstetric results.

P. W.

SURGERY: A HUNDRED YEARS AGO. Extracts from the Diary of Dr. C. B. TILANUS, afterward Professor of Surgery at the University of Amsterdam. Edited by PROFESSOR H. T. DEELMAN, professor of Pathology at the University of Gronigen, Holland. Translated from the Dutch by JOSEPH BLES. Pp. 156; illustrated. London: Geoffrey Bles, 1925. Price, 6s.

"THIS collection of letters, written during a tour made by three young Dutch doctors in the beginning of the XIXth Century, describes operations performed by great Continental surgeons such as Dupuytren and Larrey—before the use of anesthetics and aseptics. Most of these operations were marvels of surgical skill, and were considered none the less successful if the patient happened to die from *sepsis*, as was almost invariably the case." The diary of one of them, Tilanus, has been abstracted and "introduced" by Deelman for our edification and a very entertaining account it makes. Then, as is now so often the case, the youthful students were especially interested in surgical operations, and the description of a long stay in Paris brings home all too clearly the fatal specter of sepsis and the persistence of the will-of-the-wisp of phlebotomy as a panacea. Compound fractures vied with strangulated hernias and inflamma-

tion of the bowel as "captains of the men of death" and unfortunate indeed was the sick one who perforce fell into the hands of the surgeon. The relative merits of leeches, moxæ and cupping are discussed together with an interesting description of the hospital maternity arrangements of the day. Altogether this little volume offers a pleasant interlude in the past of our profession.

E. K.

Der Elektrische Unfall. By Dr. Stefan Jellinek, A.O. Professor der Elektropathologie an der Technischen Hochschule in Wien. Pp. 168; 50 illustrations. Third Edition. Leipzig and Wien: Franz Deuticke, 1931. Price, 8 M. (12s); 10 M. (15s.) bound.

Two more editions since this book first appeared in 1924, is a good record for such a specialized subject. Since then, also, it has become necessary to add chapters on accidents caused by the telephone, Roentgen ray, radium, explosions due to electricity and atmospheric conditions. In short space one can find a useful consideration of such topics as misconceptions and errors concerning electrical accidents, grounding and insulation, electrocution, apparent death, postmortem findings and methods of treatment. With the greatly increased contact of the public with electric contrivances of all sorts, such a work is most timely. E. K.

Early Theories of Sexual Generation. By F. J. Cole, D.Sc. (Oxon.), F.R.S., Professor of Zoölogy, University of Reading. Pp. 230; 21 illustrations. New York: Oxford University Press, 1930. Price, $6.00.

As a relaxation from the preparation of a *History of Zoölogy*, the author has explored this "backwater" of his subject for the benefit of biologists. Beginning with Leeuwenhoek's discovery of the spermatozoa—"one of the major events in the history of zoölogy"—he carries us in eight chapters through the various developments of the Preformation Doctrine, Epigenesis (successive rather than simultaneous formation of parts), and Theories of Fertilization and Development.

Thus we may compare the prespermatozoal speculations by Paracelsus on generation from putrefaction with a translation of Leeuwenhoek's historic letter on spermatozoa (here first translated into English) and follow the hesitating acceptance of the significance of these bodies through succeeding centuries. The preformation doctrine is traced from Empedocles, Plato and Aristotle ("when a female mouse is dissected the female embryos appear to be pregnant") to its seventeenth century heyday. The

great Swammerdam, whose motto, "We must not surmise or invent, but discover, what Nature does, as Bacon very well says," is quoted on the title page of this book, uses the unpromising line of metamorphosis of insects to support his views that "the whole human race was comprehended in the loins of Adam and Eve," so that it must necessarily become extinct when the original supply of germ cells is exhausted. The account of the hard death of this doctrine at the hands of von Baer, literally centuries after Harvey's immortal "De Generatione Animalium," needs to be read in detail to be understood. Seldom has a mistaken scientific principle had so many eminent supporters in the face of potent opposition. The story is, indeed, an interesting one, and is here so well told that all biologists concerned with acquiring a perspective in their chosen field owe a debt of gratitude to the author. E. K.

BOOKS RECEIVED.

NEW BOOKS.

Lehrbuch der Speziellen Pathologischen Anatomie, Vol. I. By Dr Eduard Kaufmann, Ord. Professor der Allgemeinen Pathologie und Pathologischen Anatomie an der Universität Göttingen, Geheimer Medizinalrat. Pp. 990; 506 illustrations. Leipzig: Walter de Gruyter & Co., 1931. Price, Rm. 55.—.

The Note-Book of Edward Jenner. With an Introduction on Jenner's work as a Naturalist. By F. Dawtrey Drewitt, M.D. (Oxon.), F.R.C.P., formerly on the Committee of the British Ornithologists' Union and on the Council of the Zoölogical Society of London. Pp. 49; 1 illustration. New York: Oxford University Press, 1931. Price, $1.25.

An Introduction to Gynecology. By C. Jeff Miller, M.D., Professor of Gynecology, Tulane University School of Medicine. Pp. 327; 117 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $5.00.

Egypt: The Home of the Occult Sciences: With Special Reference to Imhotep, the Mysterious Wise Man and Egyptian God of Medicine. By T. Gerald Garry, M.D., M.Ch., M.A.O., M.B.E., Senior Physician, Anglo-American Hospital, Cairo; Physician, Royal Terme, Montecatini. Pp. 93. London: John Bale Sons & Danielsson, Ltd., 1931. Price, 7/6d.

Collected Papers of The Mayo Clinic and The Mayo Foundation, Vol. 22, 1930. Published May, 1931. Edited by Mrs. Maud H. Mellish-Wilson, Richard M. Hewitt, B.A., M.A., M.D., and Mildred A. Felker, B.S. Pp. 1125; 234 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, $13.00.

A Clinical Study of Addison's Disease. By Leonard G. Rowntree, M.D., and Albert M. Snell, M.D., Division of Medicine, The Mayo Clinic and The Mayo Foundation. Pp. 317; 41 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, $4.00.

Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus. By Louis A. Buie, B.A., M.D., F.A.C.S., Section on Proctology, The Mayo Clinic, and Associate Professor of Surgery, The Mayo Foundation. Pp. 178; 72 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, $3.50.

The Surgical Clinics of North America, Volume 11, No. 3 (New York Number, June, 1931). Pp. 239; 73 illustrations. Philadelphia: W. B. Saunders Company, 1931.

The Medical Clinics of North America, Volume 14, No. 6, and Index Volume (New York Number, May, 1931). Pp. 300; 305 illustrations. Philadelphia: W. B. Saunders Company, 1931.

International Register of Spas and Medicinal Waters. Pp. 20. London: Headley Brothers, 1931. Price, 1s.

Clinical Dietetics. By HARRY GAUSS, M.S., M.D., F.A.C.P., Instructor in Medicine, University of Colorado, School of Medicine; assisted by E. V. GAUSS, B.A., formerly Assistant Dietitian, Presbyterian Hospital, Denver. Pp. 490; 59 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $8.00.

Fighting Disease with Drugs. A Publication of The National Conference of Pharmaceutical Research. Edited by JOHN C. KRANTZ, JR., with an Introduction by DR. JAMES H. BEAL. Pp. 230; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, $2.00.

Accidental Injuries. By HENRY H. KESSLER, A.B., M.D., F.A.C.S., F.A.P.H.A., Medical Director, New Jersey Rehabilitation Clinic. Pp. 718; 157 illustrations. Philadelphia: Lea & Febiger, 1931. Price, $10.00.

International Studies: The Prevention of Disease. Conducted for The Milbank Memorial Fund, Vol. 2, Belgium, France, Italy, Jugo-Slavia, Hungary, Poland, Czecho-Slovakia. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 249. Baltimore: The Williams & Wilkins Company, 1931.

Clinical Observations on the Surgical Pathology of Bone. By DAVID M. GREIG, M.B., C.M., F.R.C.S. (EDIN.), F.R.S.E., Conservator of the Museum of the Royal College of Surgeons of Edinburgh. Pp. 248; 224 illustrations. Edinburgh: Oliver & Boyd, 1931. Price, 30/- net.

Pediatric Education. Section on Medical Service. Committee on Medical Care for Children. Report of the Subcommittee on Medical Education. BORDEN S. VEEDER, Chairman. Presented at Meeting of Section on Medical Service, Washington, D. C., February 20, 1931. Pp. 109. New York: The Century Company, 1931.

The findings of the Subcommittee on Medical Education is presented in this pamphlet together with their recommendations as regards both undergraduate and postgraduate instruction in this phase of medical science which has heretofore been grossly neglected for a subject so valuable to the welfare of the Nation. No school can give an adequate course in diseases of children and its allied branches without sufficient and properly equipped hospitals and clinics, manned by efficient and experienced professors and assistants. The curricula are outlined together with the recommendation of the number of hours to be devoted to this branch. It is further recommended that the teaching of pediatrics should be carefully studied for the purpose of making improved recommendations at a subsequent time. A. S.

NEW EDITIONS.

Hypertension and Nephritis. By ARTHUR M. FISHBERG, M.D., Associate Physician to Beth Israel Hospital and Adjunct Physician to Mount Sinai Hospital, New York City. Pp. 619; 38 illustrations. Second edition, thoroughly revised and enlarged. Philadelphia: Lea & Febiger, 1931. Price, $6.50.

Recent Advances in Pulmonary Tuberculosis. By L. S. T. BURRELL, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Senior Physician to Royal Free Hospital. Pp. 240; 49 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, $3.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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The Pathologic Physiology of Pellagra.—A series of five papers on this extremely important disease has recently been published by TURNER (*J. Clin. Invest.*, 1931, **10**, 61). These papers represent a very thorough study of the disturbed physiology of a disease which is perhaps as important a disease from the point of view of the morbidity-mortality rate and economic loss as any disease which occurs south of the Mason and Dixon Line. A very large number of these cases are recognized each year in the far south and a very considerable number of them, at least in the early stages, go unrecognized. In this study of Turner's the first paper deals with detailed clinical data of 42 patients—sex, age, presence or absence of skin lesions and the severity, occurrence of diarrhea, sore tongue, psychoses and neuritis are considered in a most comprehensive table. Other clinical data are also included. The laboratory studies are based on estimations of the blood volume, plasma volume, red blood cell volume, as well as that of the packed red blood cells. Serum albumin, globulin, as well as the blood calcium, inorganic phosphorus, chlorids, CO_2 capacity of the plasma and total fixed base, are included. The second paper deals more in detail with the studies made on the serum albumin and globulin. In this group of patients it was found that there is a marked tendency for an extremely low serum albumin concentration which persists for a considerable period of time after the usual evidences of the disease have gone and despite a diet which is considered adequate. Turner attributes this to disturbed digestion with a low absorption of proteins as a result of injury of the digestive system by the disease. The serum protein determinations aided considerably in estimating the severity of the disease and in furnishing a criterion of cure. Paper No. III details the studies which were made upon serum calcium and phosphorus. Of particular interest in this communication is the hypothesis advanced that serum calcium concentration abnormalities in pellagrins are related in some way to disturbances of the nervous system. This may be causal or incidental. The next paper has to do with the serum electrolytes and acid-base equilibrium. The diminution in serum electrolyte concentra-

tion apparently is of considerably more importance than disturbance of acid base equilibrium in the pathologic physiology of this disease. The diarrhea and at times the vomiting that occur in this disorder seem to be the factor chiefly responsible for the low electrolyte concentration of the blood serum of the pellagrins. The last paper in the group is a study of the circulating blood volume in 41 pellagrins. In this group of patients the findings were as follows: 68 per cent of the group showed plasma volumes below normal and 32 above normal. The median was −4 per cent deviation. The red cell volumes in 95 per cent of cases were below normal, with a median of −35 per cent deviation. The total blood volumes in 82 per cent of these pellagrins were below normal, with a median of −17 per cent deviation from ideal. Probably the most interesting clinical observation from these studies on the blood volume lies in the suggestion that certain skin abnormalities in chronic pellagra may be the result of deprivation of the skin of an adequate blood supply for a considerable time, although there is a concomitant (presumably) engorgement of the abdominal viscera. It is impossible to go into the details of these studies, but any one who is interested in a most remarkable disease whose manifestations differ in many ways from the usual run of disease, will find these studies stimulating as well as instructive.

SURGERY

UNDER THE CHARGE OF
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Derangements of Semilunar Cartilages.—MacCausland (*Ann. Surg.*, 1931, **93**, 649) states that the removal of a semilunar cartilage according to his technique (described in full in his paper) is followed in the majority of cases by a result entirely satisfactory to the patient. The best results are obtained in cases of young adults when the offending cartilage is removed within a short time of the trauma. A guarded prognosis must be given in cases with any arthritic tendency, which includes cases of long standing that show definite hypertrophic changes at operation and cases of older patients, that is those beyond middle life. Particular attention should be given to the treatment of mild injuries. If a slightly damaged cartilage is neglected it exposes the joint to progressive arthritic lesions. The most reliable diagnostic features are a definite history of trauma; recurrent periods of disability with local pain, slipping, effusion and swelling, initiated usually by some minor injury or twist; acute local tenderness at the point of attachment of the cartilage where the damage is located with a tendency for the tenderness to persist at this point; locking, that is, sudden inability to extend the joint fully; the absence of the cartilage thrust; the presence of an early pathologic lesion, such as tuberculosis or syphilis, must be borne in mind when operation for the removal of the cartilage is advised.

The Use of Exploring Needles and Shadow Casting Media in the Diagnosis of Hepatic and Perihepatic Abscess.—Wilmoth (*Ann. Surg.*, 1931, **93,** 722) says that the exploring needle has a definite place in the diagnosis of hepatic and perihepatic abscess, and when used for injection of iodized oil the definite location, size and shape of the abscess can be determined. The site of the abscess is not entirely sufficient datum for successful treatment, but the extent of the cavity in all directions is important. The aspirating needle cannot be used with safety in the left lobe of the liver, in left perihepatic spaces. The exploring needle can be used without a general anesthetic. In the acutely ill patient the procedure gives no appreciable shock and the subsequent incision and drainage, if indicated, can be by the route that is shortest and least shocking. The spinal puncture needle or similar blunt needle adds to the safety of the procedure. The aspirating needle is of value both in diagnosis and in treatment of amebic abscess of the liver, or of those that have extended into the perihepatic spaces, provided secondary infection has not occurred. The presence of pyogenic organisms is an indication for incision and drainage. There is usually only one satisfactory route of approach to a hepatic or perihepatic abscess, and that route can be determined in the majority of cases by the definite localization of the boundaries of the cavity after injection of some opaque substance.

Twenty-five Years' Study and Survey of Syphilis.—McDonagh (*Urol. and Cutan. Rev.*, 1931, **35,** 123) writes the period opens with the advent of the syphilitic trias and closes with the unitary view of the disease. The trias includes the discovery of the Spirochæta pallida, the Wassermann reaction and arsenobenzene. When it was seen how quickly the signs and symptoms of syphilis vanished under arsenobenzene it was no longer thought necessary to keep the patient under treatment for two or more years. The treatment became symptomatic and its efficacy appeared to be confirmed by the number of fresh infections which occurred. The next stage was the increase of neurorecurrences. In fact, the incidence rose as the treatment became more spasmotic and gauged by the Wassermann reaction. Later, when it was found necessary to make the treatment more intensive and continuous, no fresh infections occurred, proving that what were considered at first to be fresh chancres were really recurrent chancres. Treatment alone does not diminish the incidence of an infection. Waves suggestive of an increase of syphilis appear from time to time, and the advent of another wave would render it again one of the biggest scourges. Syphilis sleeps—it is not dead or dying. What is most to be deplored is the gradual disappearance of clinical diagnosis, which brings even worse in its wake, the inability of the physician to learn his patient. Clinical acumen is the highest attainment to which a physician can aspire and learning and knowing the patient are going more than half way to ridding him of disease. Despite all the so-called "epoch-making" discoveries of recent years, the present state of medical science is not one to be proud of and the outlook to the author is far from hopeful.

Infective Granuloma.—Mack (*Surg., Gynec. and Obst.*, 1931, **52,** 672) reports that infective granulomata are far more frequent than the

literature on this subject would lead one to believe. The condition is directly due to a low-grade infection, causing an impairment to the circulation, or to an impairment of the circulation followed by a low-grade infection. In either case there is an inflammatory reaction characterized by a necrosis and a reparative process acting and reacting with a gradually increasing building up of an inflammatory mass, until a granuloma reaching even the size of a coconut has formed. Occasionally the reparative process predominates early in the condition, and one finds a constricting or stenosing granuloma. Infections within the gastrointestinal tract, such as appendicitis or diverticulitis, ulcers either within the stomach or in the intestine, foreign bodies within the bowel lumen, in the wall of the bowel or lying in the abdomen, such as purse-string sutures, lap pads or instruments left in the abdomen, splinters penetrating into the abdomen, may become the nucleus for the foundation of an infective granuloma. Trauma is a frequent cause for the condition, especially trauma, which results in a tear of the mesentery which allows foreign material to remain in the abdominal cavity or which may cause an undiagnosed and nonfatal perforation or laceration of the intestinal wall. Extraperitoneal inflammations may spread to or involve the gastrointestinal tract in the granulomatous mass. The diagnosis of carcinoma is most frequently made when an infective granuloma exists. Many of our recovered cases of inoperable carcinoma of the gastrointestinal tract have undoubtedly been granulomata. A more careful study of all cases of infective granuloma will enable an increasing number of correct pre-operative diagnoses to be made. The etiology, the similarity in the chain of symptoms, the characteristic findings at operation and the ability to make the diagnosis on histologic study warrant considering infective granuloma as a definite disease entity. In the presence of a tumor mass within the abdomen the possibility of an infective granuloma should always be taken into consideration in making the diagnosis.

THERAPEUTICS

UNDER THE CHARGE OF

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The Treatment of Angina Pectoris With Glucose.—HASSENCAMP (*Zeitschr. f. Kreislaufforsch.*, 1931, **23**, 132) discusses the probable mechanisms involved in Büdingen's intravenous injections of glucose solutions in the treatment of angina pectoris. He points out that Büdingen's original conception of the cardiac condition resulting from

hypoglycemia was entirely erroneous, due to errors on the part of the laboratory in the determination of blood sugar. Nevertheless the use of glucose has proved a valuable therapeutic procedure in many cases of angina. First, by supplying an excess of readily available sugar to the heart muscle; second, probably by alterations in the physical properties of the cells there are colloidoclastic and osmotic effects, and finally, through the relaxation of spasm in the smaller coronary branches. In treatment he employs freshly made solutions of pure glucose in freshly distilled water, beginning with an injection of approximately 30 cc. of a 10 per cent solution and increasing to 50, 80, 100, 150 and even at times to 200 cc. of a 10 to 20 per cent solution. He emphasizes that no fixed schedule of doses can be established, but that each patient must be treated according to his individual responses and that many patients have definite upper limits to the dose tolerated, above which the injections produce constitutional symptoms. Customarily he administers three injections weekly, though at times only two can be given. Better results are obtained from the use of the larger volumes of more dilute solution than from smaller volumes of more concentrated solutions. In those patients whose angina pectoris is complicated by other cardiac symptoms, namely, congestive failure and renal disturbances, the doses should range from 10 to 50 cc. of a 15 to 20 per cent solution, and it is frequently of great value to add from 0.2 to 0.3 mg. of strophanthin to the solution or, where a diuretic is needed, ½ cc. (50 mg.) of theobromin ethylenediamin. Even in cases complicated by diabetes it is possible to employ the sugar treatment with excellent results and without detriment to the diabetes. In general the sugar treatment must be continued from four to six weeks to obtain fully satisfactory results but, when secured, these frequently last for many months, even up to several years. The most satisfactory results are obtained in patients suffering from the angina of effort, while those with the angina of rest and angina complicated by cardiac weakness or renal insufficiency give less uniformly satisfactory results and results which, in general, are less permanent.

Medical Opinions on Circulatory Hormone Preparations.—In an effort to secure some trustworthy conclusions concerning the value of several of the so-called hormone preparations derived from the heart, voluntary muscle and certain glandular organs such as the liver and pancreas, R. VON DEN VELDEN (*Deutsche med. Wchnschr.*, 1931, **57**; April 10, page 619; April 17, page 672; April 24, page 712 and May 1, page 753), records and analyzes the replies to a questionnaire from more than 40 leading internists in Europe. It is evident, from the answers secured, that opinion as to their therapeutic value is highly contradictory. Despite the fact that certain investigators have apparently been able to demonstrate biologic activity of these preparations when tested upon animals and surviving animal organs, the majority of clinicians feel that these preparations exert no influence upon the cardiac rate or rhythm or upon the electrocardiogram and the majority finds that they are without influence upon the action of digitalis upon the heart of man. Some investigators report more or less satisfactory results from their use in angina pectoris, while the majority find them either to be without effect in this condition or distinctly inferior to the

usual drugs employed such as the nitrites and the xanthin derivatives. The same conflict of opinion concerning their observed effects upon elevated blood pressure is expressed by the various internists, although here many are inclined to believe that they are of definite value in lowering the blood pressure in the condition of essential hypertension, particularly where the pressure normally shows wide spontaneous variations. Both in the case of angina and of essential hypertension however, many of those who record some favorable results express the opinion that these are limited to those patients who are definitely of the neurotic type and that the results can be explained on the basis of psychotherapy, similar results being frequently obtained in the same patients from other forms of treatment. The author states it as his opinion that there is some promise in this form of therapy but scarcely dares to go further in its recommendation. He believes that its clinical use constitutes the treatment of ill patients with very uncertain remedies. In addition to this great uncertainty in the action of these substances, attention must be called to the fact that many clinicians have observed distinctly unfavorable side actions following their administration, especially following their intravenous or intramuscular injection.

NOTE.—A critical analysis of the replies indicates that these agents should not be accepted for clinical use in the present state of their development. It seems certain from the evidences presented that they are extremely untrustworthy, if indeed they have any definite actions upon the circulation other than those common to nonspecific protein split-products.—EDITOR.

PEDIATRICS

UNDER THE CHARGE OF
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Impetigo Contagiosa Neonatorum.—SWENDSON and LEE (*J. Am. Med. Assn.*, 1931, **96**, 2081) state that impetigo contagiosa neonatorum in nurseries for the newborn has become a serious problem of the modern hospital. It is practically impossible to prevent the occurrence of sporadic cases in nurseries. Constant vigilance for the detection of pyogenic infections in attendants and nurses and patients, and a nursery technique discouraging the development of pyodermic infections in newborn infants, is necessary in order to prevent epidemics of the disease. Epidemics are best controlled by means of a three nursery system which allows of segregation of infected babies, exposed babies and babies that have not been exposed from one another. They recommend a dry treatment of the lesions with the avoidance of the use of ointments. In this technique a bath is given every other day. Very little soap should be used and the skin should be dried by patting rather than by rubbing. After the bath the entire body should be

heavily coated with a dusting powder containing mercurous chlorid, 3 parts; talcum, 2 parts, and zinc oxid, 1 part. On the alternate days the babies should be examined for skin lesions, the buttocks should be cleansed with sterile oil and the dusting power again applied. The powder stains the clothing gray. If irritation develops talcum should be temporarily substituted. Excessive warmth and moisture of the skin should be avoided by dressing the babies lightly.

Inhalation Method of Resuscitation from Asphyxia of the Newborn.—HENDERSON (*Am. J. Obst. and Gynec.*, 1931, **21**, 542) recommends the simplest apparatus, consisting of a small cylinder of a mixture of oxygen and 7 per cent carbon dioxid, with a mask to enclose the face and a rubber bag of only 2- or 3-liter capacity, with a valve or stopcock at the end. The bag is filled and the cylinder cut off. The mask is held on the face while the bag is squeezed to make a gentle pressure sufficient to cause a succession of slight dilatations of the baby's lungs. Then, as spontaneous breathing begins, the inhalation is continued, or, if desired, mouth-to-mouth dilatation may be used and then the inhalation administered. It is the inhalation and its stimulating effects on natural breathing rather than any form of artificial respiration that is most important. This inhalation should be given several times a day for five or ten minutes for several days. He recommends its use not only for asphyxiated babies but also for normal babies. The object of this latter recommendation is to insure full dilatation of the lungs. When this inhalation is universally adopted instead of the old method of making the child cry, the large number of babies that die of pneumonia consequent to a persisting atelectasis will be saved as well as those that can be resuscitated most effectively by this method from primary birth asphyxia. The essential point regarding birth asphyxia is that, as a result of diminished blood supply to the brain during prolonged labor, the sensitiveness of the respiratory center is depressed. In the normal child the respiratory center is stimulated, as soon as the placental circulation slows down, by the carbon dioxid formed in the child's own body. In the asphyxiated child, although there may be more carbon dioxid than normally, the center is so depressed that this stimulus is insufficient to excite natural breathing. When a sufficient quantity of carbon dioxid is supplied to the lungs the center responds normally.

Prognosis of Acute Glomerular Nephritis in Children.—GUILD (*Bull. Johns Hopkins Hosp.*, 1931, **48**, 193) studied 34 patients from 1 to 12 years after an acute attack of glomerular nephritis. He found that in this condition in children the prognosis is good and, in general, the younger the child the better the prospects of complete recovery. Albuminuria may persist for years without impairment of general health or kidney function. It may also disappear completely after it has been present at least as long as a year. Children who have once had acute nephritis stand subsequent infections without greater liability to complicating renal disease than is shown by children who have never had nephritis. Although many of the patients are now entirely normal in spite of neglect of foci of infection following the attack of

nephritis, the fact that several of those now showing some abnormality are among those neglected suggests that it is wise to attend to such foci promptly in all cases. It is of the utmost importance to follow those patients with albuminuria to determine the ultimate results.

Treatment of Acute Cerebral Complications of Nephritis.—ALDRICH (*Am. J. Dis. Child.*, 1931, **41**, 1265) studied the clinical records of 28 patients who showed cerebral symptoms in the course of hemorrhagic types of nephritis. He attempts to explain the behavior of these patients on this hypothesis. Owing to an intoxication that is probably the cause of the nephritis, the tissues, including those of the brain, take on water and become edematous. This water is considered to be held in chemical combination with the tissue cells. The resulting edema of the brain causes increased intracranial pressure, a compensatory rise in the blood pressure and clinical symptoms. The general increased affinity of the tissue cells for water results in oliguria and usually in subcutaneous edema. When large amounts of fluid are given there is a tendency to dilute the toxins and to provide free water for their elimination through the kidneys. Thus paradoxically, the administration of water may reduce edema. In this process, when the cerebral edema is decreased, the intracranial pressure and the systemic blood pressure fall, giving relief from the cerebral symptoms. Following this, as more water becomes available for excretion, diuresis takes place. When the onset of coma makes the adequate administration of fluid impossible, intravenous injections of strongly dehydrating salts, such as magnesium sulphate, shrink the cerebral tissues, leading to prompt relief from the symptoms and allowing the administration of fluids by mouth. The administration of magnesium sulphate by mouth in large doses seemed to hasten recovery, and did not cause loose stools in edematous patients until the symptoms had disappeared. It is believed that when given orally this salt acts in the same manner as when given intravenously.

Comparative Studies on Calcium Gluconate and Other Calcium Salts.—LIEBERMAN (*J. Am. Med. Assn.*, 1931, **97**, 15) studied the effect of calcium gluconate on human beings and dogs when given orally, subcutaneously and intravenously. This compound can be given in repeated and adequate amounts subcutaneously without causing either irritation or necrosis. Three or 4 gm. a day after meals seemed to be the proper dose for an adult. Blood calcium attains its maximum elevation within an hour after subcutaneous or intramuscular administration of calcium and within four hours after being given orally. Urinary calcium appears to be a qualitative index of the state of the blood calcium level. Whether this is true in all pathologic states remains to be seen. A urinary value of about 10 to 20 mg. per hour appears to be most desirable in avoiding either a hypercalcemia or a hypocalcemia. Intravenous calcium therapy is dangerous because of the danger of sudden intravascular clotting and death. Highly suggestive digitalis-like effects of calcium were observed, but could not be explained.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF
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Apparent Specific Effects of Sodium Iodide in Herpes Zoster.—RUGGLES (*Arch. Dermat. and Syph.*, 1931, **23**, 472) reports 15 cases of herpes zoster favorably influenced by the intravenous administration of sodium iodid in 2-gm. doses in 20 cc. of sterile water, given on the first, second, fourth and seventh day of observation. The early relief from pain and rapid involution of the skin lesions are quite striking in a number of the cases. The author claims no originality for the method and can advance no satisfactory explanation of its rationale, but offers it as a distinctly valuable addition to the therapy of extensive painful cases of zoster.

Cutaneous and Mucosal Relapse in Early Syphilis and Its Differentiation from Reinfection.—STOKES, COLE, MOORE, O'LEARY, PARRAN and WILE (*Ven. Dis. Inform.*, 1931, **12**, 55) have studied 5952 cases of early syphilis from their five respective clinics to ascertain the frequency, infectiousness, time and appearance, localization and morphology of relapse. Three hundred and sixty cases of mucocutaneous relapse and 40 supposed reinfections were thus brought to light, showing that relapse is one-fifth as frequent as chancre and reinfection one-ninth as prevalent as mucocutaneous relapse. The public health import of these facts is evident when one realizes that relapse is less conspicuous than chancre and consequently more easily ignored by patient and contact. Some of the more important conclusions of the paper are as follows: (1) The proportion of relapse is less in cases seropositive in the primary stage at the onset of treatment or in florid secondaries when they began treatment in the first year of their disease than in cases which are seronegative at the outset; (2) 68.6 per cent of mucocutaneous relapse was extragenital and 31.4 genital; (3) 62 per cent of relapse lesions are potentially infectious; (4) mucocutaneous relapse appears (91 per cent) in the first 2 years after treatment and 85 per cent of it occurs in the first 2 years of the disease; (5) arsphenamin-mercury therapy is followed by 9.6 per cent of relapse as compared with 3.6 per cent under arsphenamin-bismuth therapy; (6) the proportion of mucocutaneous relapse is greatly reduced after the ninth to the fifteenth arsphenamin injection; (7) the criteria for the acceptance of reinfection are reviewed and none in the present supposed series of reinfections are found to be completely acceptable. A small proportion only satisfy even moderately strict requirements.

GYNECOLOGY AND OBSTETRICS

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Roentgen Therapy of Uterine Cancer.—At the Erlangen Roentgen Institute between 1915 and 1925 there were 956 cases of uterine cancer treated with Roentgen rays which are analyzed in a paper presented by WINTZ (*Ann. Surg.*, 1931, **93**, 428). The treatment was based on the principle of applying the cancer dose, if possible, at one sitting or in the course of 48 hours. The results of treatment show that in carcinoma of the cervix there were 125 operable cases with 60 per cent 5-year cures and 712 inoperable cases with 12 per cent 5-year cures. Of the adenocarcinomas of the corpus there were 59 operable cases with 69.5 per cent 5-year cures and 160 inoperable cases with 8.3 per cent 5-year cures. Since 1921 the statistics have been even better than those mentioned, due largely to the use of copper treatment which produces secondary radiation in the tissues by metallic particles introduced by means of iontophoresis. He describes in detail the technique of this procedure. One of the reasons that this copper treatment has improved the results is that it accomplishes a deep disinfection of the tissues and it is well known that infected tissues do not respond to irradiation nearly so readily as comparatively uninfected tissues. He points out the importance of living conditions and systematic after care in patients treated by irradiation. In comparing two series of cases he found that of those in good circumstances 46 per cent were cured whereas of those in poor circumstances only 32 per cent were cured. The after care of these patients must aid the body to eliminate the products of degeneration. Mechanical cleansing is obtained by disinfecting irrigations. For those masses of decayed cells which have been swept off by the blood stream, sulphur is administered by mouth or intravenously. If the systemic condition is poor, arsenical preparations are used. The effect of altitude in accelerating metabolism is used to assist in eliminating degenerative products.

Early Diagnosis of Cervical Cancer.—Several years ago we called attention to a new method developed by Schiller for the early detection of cancer of the cervix which was based upon the application of an iodin solution to the suspected cervix. He showed that normal tissues took the iodin stain whereas diseased tissues remained iodin negative. However, we are careful to state that all iodin negative tissues were not carcinomatous but were to be regarded as suspicious. This phenomenon was explained as being due to a deficiency in the glycogen content of atypical proliferating epithelial cells. This subject has been investigated by ISSACHANOW (*Zentralbl. f. Gyn.*, 1931, **55**,

1215) who believes that it has been of real assistance in the early diagnosis of cancer. By means of statistical tables he shows that he has been able to detect early carcinoma in more than twice as many cases by this method as by the simple biopsy without the use of the iodin stain. In the technique which he has followed the patient is given a vaginal douche after which a speculum is inserted and the cervix is dried with cotton and painted with a 5 per cent tincture of iodin. The major portion of the cervix will be stained brown but in the suspicious cases there will be clear points (iodin negative) within this dark-brown field. This part of the field is either curetted away or removed by excision, taking some of the apparently healthy tissue with it. If a suspicious polyp be present, it is drawn down by forceps and removed at the base, being careful to get beyond the pedicle. The suspicious tissues are then examined microscopically for the final diagnosis. It would seem that by the use of this method as a routine many early cases would be detected which otherwise might not be regarded serious enough to demand a biopsy. (This is a vauluable adjunct to the diagnosis of cervical cancer, but as pointed out by Issachanow it is by no means a substitute for the histologic method. One of the difficulties sometimes associated with biopsy is making certain that the tissue has been secured from the the proper area and for this reason trachelectomy is preferable in certain cases. C. C. N.)

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Arcus Senilis as an Accompaniment of Cardiovascular Disease.—Scott (*South. Med. J.*, 1931, **2**, 24, 165) observed arcus senilis in 179 (6.2 per cent). Histologically, arcus senilis is a deposit of fatty substances and perhaps, also, of lime and hyalin particles in the corneal parenchyma. It occurs usually coincident with other changes indicative of old age, but it may appear even in childhood. Of 2891 patients of all ages examined in a cardiac clinic 63 per cent were white and 36 per cent colored, but of the arcus senilis cases 107 (59 per cent) were colored. One hundred and fifty-two of 780 patients with arteriosclerosis in some form showed definite arcus senilis (19 per cent). Thus, 84 per cent of the cases of arcus senilis were subject to arteriosclerotic changes and only 4 per cent showed no signs of cardiovascular disease. Of the arcus senilis cases 48 per cent belonged to the laboring class; the ages varied from 31 to 95 years and 64 per cent were between the

ages of 51 and 70 years. The frequency and predominance of arcus senilis among colored people is striking. Arteriosclerosis is quite commonly associated with this form of corneal degeneration and may be an etiologic factor; but the majority of arteriosclerotic patients do not have arcus senilis. Faulty nutrition and physical degeneration within an ethnic group may explain its frequency in negroes. Arcus senilis may then be looked upon as one of the indices of racial degeneration.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The Value of the Schilling Hemogram in the Otologic Infections.—In a detailed account of observations made on 9 cases ALDEN and DE MOTTE (*Ann. Otol., Rhinol. and Laryngol.*, 1931, **40**, 95) feel that the consistent manner in which the hemogram findings have paralleled the clinical features makes this laboratory aid of distinct value in the study of the otologic infections. Further confirmation is given in the fact that the stab cell count offers a much more reliable index of the patient's condition than does the polymorphonuclear percentage of the total number of the white blood cells, and particularly in children, than the pulse and temperature variations. The hemogram must be considered as a distinct advance in the interpretation of various blood findings, but cannot be expected to accurately differentiate between such closely allied conditions as acute suppurative otitis media and acute suppurative mastoiditis. It is also of far more value when daily or very frequent observations can be made under a strict set of conditions. It is by no means introduced to supplant clinical investigation, but to corroborate it. Finally, the correct valuation of such laboratory criteria permits an individualization of treatment according to the given case, because it furnishes data so significant as to make pathologic details more comprehensible and the results more uniformly successful.

Allergy in the Middle and the Internal Ear.—In these days when hypersensitiveness is in the saddle many interesting and important phenomena are being encountered. PROETZ (*Ann. Otol., Rhinol. and Laryngol.*, 1931, **40**, 67), after a bibliographic review and a clinical study of a limited series of cases, concludes that localized allergic reactions may simulate other aural diseases by the mechanical reactions of edema upon the tissues of the tympanum and labyrinth. They may be differentiated by the nature of the onset, often accompanied by allergic manifestations elsewhere by a careful history of the patient's sensitivities, and sometimes by the occurrence of eosinophilia.

Histopathology and Bacteriology of Sinusitis: With Comments on Postoperative Repair.—Based on a study of tissues secured from 15 persons, KISTNER (*Arch. Otolaryngol.*, 1931, **13**, 225) noted epithelial or connective-tissue hyperplasia as a common structural change of the mucosa in chronic latent or nonpurulent sinusitis—regardless of the underlying etiologic factor, bacterial, allergic or avitaminosis. Pathogenic microörganisms were found in the tissues of those cases where the sinusitis was associated with systemic disease. The sinus and nasal mucous membranes differ greatly in histologic structure, organization and appearance. After complete destruction the sinus mucosa does not regenerate its structures. Granulation tissue organizing into typical scar tissue and bone proliferation are basic features of the reparative process. The type of epithelium which eventually covers the fibrous tissue depends on the character of and distance from the ancestral epithelium. Cultures from 400 sinuses usually yielded a mixture of organisms. Streptococci predominated (94.5 per cent). In the order of frequency, staphylococci, Micrococcus catarrhalis, pneumococci, Bacillus Friedländer, Bacillus influenzæ, Bacillus coli, diphtheroids and streptothrix were found.

RADIOLOGY

UNDER THE CHARGE OF
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Roentgen Treatment of Metastasis to the Vertebræ and the Bones of the Pelvis from Carcinoma of the Breast.—Metastasis from carcinoma of the breast reaches the pelvic and vertebral bones probably by a combination of aberrant and reflux spreads through the lymphatics and is often accompanied by an inflammatory reaction of noninfectious origin, in the opinion of LEDDY (*Am. J. Roent. and Rad. Therap.*, 1930, **24**, 657). The most common symptom of such lesions is pain in the right sciatic nerve. The distribution and type of metastasis, in the group of 40 cases studied by Leddy, have no relationship to the primary tumor. Treatment by Roentgen rays, by an effect on both the inflammatory and malignant cells in the metastatic growths, produces analgesia, often complete and of month's duration, and is the best method of palliating a hopeless case. But sooner or later Roentgen therapy loses its initial effectiveness. Usually one or two recurrences of symptoms due to reactivation of the metastasis in bone may be handled successfully, but eventually all treatment is useless.

Roentgen-Physiologic Studies of the Gall Bladder in Dogs.—REWBRIDGE and HALPERT (*Am. J. Roent. and Rad. Therap.*, 1930, **24**, 634) injected lipiodol or brominol into the gall bladders of 26 healthy dogs

after laparotomy, and made cholecystograms at intervals thereafter. The shadow of the gall bladder disappeared in most of them in from two to seventeen days, but, in 5 dogs the shadow persisted with little change until the experiment ceased. At necropsy, droplets of lipiodol or brominol were found in the gall bladder of most of the dogs in which the shadow has disappeared. From these observations the writers conclude that complete emptying of the gall bladder does not occur with each meal; furthermore they regard it as probable that complete evacuation of the biliary vesicle never takes place in the dog.

Mixed Tumors of the Parotid Gland.—These tumors of the parotid are usually mildly malignant new growths and are occasionally found in the other salivary glands or elsewhere about the face. The consensus of surgical opinion apparently favors early and radical removal of encapsulated tumors, but opposes attempts at removal of nonencapsulated growths. However, MERRITT (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 507), who has treated 10 cases by radiologic methods, believes that the treatment should be in the hands of the radiologist. He considers that high-voltage Roentgen therapy is a useful adjunct to radium. While a small encapsulated tumor may be successfully excised, the author believes from the accumulated evidence that implanted radium will accomplish equally good results. He considers a combination of surgical removal with irradiation by either radium or Roentgen ray as illogical; if the former is adequate, the latter is superfluous. Failure to destroy the tumor by irradiation at the initial attempt does not induce the increased malignancy which frequently follows inadequate surgical treatment.

Influence of Ultraviolet Light on the Glucose Tolerance of Rabbits.—Apparently little is known concerning the relation of ultraviolet light to glucose tolerances, and opposite views are held as to the effect of the former on the latter. ROOT (*Arch. Phys. Therap. X-ray, Rad.*, 1931, **12**, 153) exposed a number of normal rabbits to irradiation with a quartz lamp for periods of 10 to 25 minutes, and the results of his investigations indicated that the ultraviolet light increases tolerance for high concentrations of glucose, although the mechanism of the action remains to be determined.

The Cavity in Pulmonary Tuberculosis.—From roentgenologic studies at the Detroit Tuberculosis Sanitarium, PINNER and PARKER (*Am. J. Roentgenol. and Rad. Therap.*, 1931, **25**, 454) have developed a classification of tuberculosis cavities in the lungs which they consider an important factor in prognosis and the selection of treatment. The first type is described roentgenologically as "moth-eaten areas in infiltrated parenchyma," the appearance being due to multiple small cavities without walls. These cavities are young, so to speak, and respond readily either to artificial pneumothorax or phrenectomy. The second type comprises the round or oval cavities with a definite, fibrous wall of varying thickness. These also are relatively young, and more than 60 per cent of them will close after phrenicotomy or

pneumothorax. The third type consists of large irregularly shaped cavities, with very thick walls. About one-half of them decrease in size under appropriate nonsurgical treatment; less than one-half are diminished by phrenicotomy or pneumothorax, and none close after such treatment. In short, therapeutic success in the surgical treatment of cavities is in inverse ratio to the amount of demonstrable fibrosis in the cavity walls.

The Present Status of Electrocoagulation of Tonsils.—The relative advantages and disadvantages of surgical removal and electrocoagulation are compared by NOVAK (*Arch. Phys. Therap., X-ray, Rad.*, 1931, **12**, 226). He arrives at the conclusion that, although surgical removal is not an ideal technique, in that it is liable to difficulties and complications, it is at present the best available technique. The removal of tonsils by diathermy is not devoid of risks, and the proper technique is not easy to learn or execute. A properly executed surgical tonsillectomy in a neat, swift, complete, workmanlike job in the ordinary case. Under similar conditions, diathermic destruction is slower, lacking in the precision and control characteristic of good surgery, and there is always the unpredictable factor of the depth of penetration obtained. Nevertheless, electrocoagulation has its place as an adjunctive method, and is the operation of choice in certain selected cases, especially those which are poor operative risks.

The Practical Value of Radium in the Treatment of Certain Fibroid Tumors of the Uterus.—From his experience with 286 cases treated by intrauterine application of radium, after diagnostic curettage in all save 2, CRUTCHFIELD (*Radiol. Rev.*, 1931, **53**, 89) is of the opinion that this treatment is the method of choice in menorrhagia associated with uncomplicated fibromyomata less in size than $3\frac{1}{2}$ months' pregnancy in women approaching or within the menopause. On the other hand, radium treatment is contraindicated when the tumors are larger than a 3 months' pregnant uterus; when they are complicated by lesions on the adnexa; when they produce pain or other symptoms from pressure on the bladder or bloodvessels; when they are causing cachexia by necrosis; when the tumors are increasing rapidly in size or undergoing calcareous change; when the patients are under 35 years of age; when the fibroids are associated with other intraäbdominal lesions; when the patient has an ineradicable fear of cancer; when the diagnosis is not clear. For all such cases surgical treatment is preferable.

Evaluation of Electrosurgery of the Tonsils.—In the opinion of BALMER (*Arch. Phys. Ther., X-ray, Rad.*, 1931, **12**, 10) electrocoagulation is the superior method for removal of postoperative tonsillar tissue and adhesions, lingual hypertrophy and varix, and for the extirpation of the faucial tonsil in the presence of certain diseases, such as hemophilia, anemia and the serious affections of the lung, heart and kidney. It is not applicable to children or to nervous or refractory patients. No method of tonsil removal is ideal under all circumstances, but the combination of surgery and electrocoagulation is a means of approaching the ideal.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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The Treatment of Postencephalitic Children in a Hospital School.—Bond and Appel (*Am J. Psychiat.*, 1931, **10**, 815) present an encouraging study of the treatment of 48 postencephalitic children in a hospital school. There were 14 controls in the group, bringing the total number of children presented to 62. The results they tabulated as follows:

	Post-encephalitic.	Controls.
Good	7	1
Doubtful	7	1
Poor	6	2
Still in classes	22	8
Feebleminded	6	2

They remark that "these figures show that in 20 postencephalitic (excluding the feebleminded) sent home 7 had good results, or 35 per cent, as compared with the total failure of family placement, as reported by Healy." In this paper the authors describe in a general way the manner in which their work was carried out, noting that more detailed reports of various phases of the work would be reported later. The hospital school in which the work was done possessed adequate living quarters and recreational facilities, and was connected with separate men's and women's departments of the Pennsylvania Hospital for Mental and Nervous Diseases. The personnel of this institution consisted of: A nurse in charge trained in psychiatric nursing; graduate and student relief nurses; occasional attendants; male nurses with the boys and female nurses with the girls; a teacher, trained in special classwork, had charge of their schoolwork; occupational therapy teachers had charge of the children part of the time that they were not in school. Regular periods for a singing class were held by a music teacher. A psychologist made tests from time to time. The gymnasium and swimming pool were adequately supervised. Several psychiatrists who has special interests in children supervised and coördinated the work. The routine of the day, while not absolutely rigid, followed certain regular lines. This, it was found, eliminated much of the mischief through substitutive activity. A certain amount of free playtime was found necessary. In addition, the authors note, impersonal schedules and gross group methods were not enough—that individualizations and consideration of the separate personalities had to be added to obtain the best results. With this background to work with, the authors state that "The psychiatric nurse, trained to look upon unusual irritating and antisocial behavior with equanimity and understanding, was a

great help. The children thus found no unemotional background to their behavior in the hospital, which was in marked contrast to what they had experienced before hospital entry. . . . The children were encouraged to feel that their behavior difficulties could be cured like any other conditions for which one enters the hospital. . . . Graded schoolwork was carried on, but emphasis naturally had to be placed on individual difficulties and problems. The amount of work done was probably equal to one-half or two-thirds of that done in the ordinary grade school. The group lacked initiative and originality notwithstanding their restlessness and curiosity." The hospital point of view and plan was continuously emphasized. The workers were urged to read various books on the problems of children in order that they might understand the problems of those with whom they came in contact. A definite attempt was made to have all exhibit a spirit of optimism. An unemotional attitude toward delinquency was developed. The workers were requested to maintain an attitude of impersonal authority, and understanding and coöperation were stressed rather than criticism, discipline and punishment. In order to bring home to those in charge of the children that behavior disorders are the manifestations of difficulties in the dynamics of personality adjustments, conferences were held at varying intervals. All attended—then observations, impressions and suggestions were pooled in order that no conflicting attitudes on the part of the workers might exist. Concrete accounts of the activities of the children were then related and a general discussion of the outstanding traits or greatest problems and the best approach to the problem would conclude the conference. The authors found that "There are objections to such a formal procedure, but it gave a *modus operandi* to get all the personnel thinking on the child's personality and its problems, and his reactions in terms of his needs."

Encephalitis and Encephalomyelitis in Measles.—Terraro and Scheffer (*Arch. Neurol. and Psychiat.*, 1931, **25**, 748) report 6 cases of measles that died of central nervous system complications. These cases are presented in detail, each giving an adequate clinical summary and a very complete pathologic report. The histopathologic studies of the cases which form the major portion of the paper show that in all 6 cases the lesions of the brain were practically the same. They consisted mainly of a perivascular proliferation, formed especially of microglial elements. The microglial nature of the cell was brought out by the specific methods of silver impregnation. In some instances there were scattered elements of hematogenous nature in the perivascular areas. These elements were mainly lymphocytes and occasionally plasma cells. The perivascular hematogenous elements were "never of great importance and in some cases there was no trace of them in all the material studied." The perivascular proliferation was dominantly located in the white substance, where it formed large islands. The cortex, however, was involved by the same process, although to a much less extent. Accompanying the perivascular proliferation there was demyelinization, which formed another characteristic of the pathologic process. Lesions involving the axis cylinders in the demyelinated areas were also noted. Less characteristic was the macroglial reaction,

with both its progressive and its regressive changes. In addition, the authors point out a frequency of thrombi (red thrombi) and the occurrence of vascular changes, swelling or hyperplasia of the endothelium. This latter finding, they state, points "to a participation of the vascular system in the process, and this fact, associated with the one that most of the lesions are perivascular in topography, justifies the hypothesis that whatever noxious agent is the cause of the lesions, this agent is carried from the bloodvessels to the surrounding tissue and is favored by an abnormal permeability of the protective wall and stasis of the venous system." In addition, the authors present the three main views of the etiology of encephalitis that follows vaccinations or acute exanthematous diseases: "(1) That the lesions in the brain and cord are due directly to the action of the virus of smallpox, vaccinia or measles; (2) that they represent an allergic or anaphylactic phenomenon occasioned by the preceding illness; (3) that they are caused by an unknown virus or toxin which is in some way empowered by the exanthematous disease to attack the nervous system." They present the proof both for and against these theories and finally conclude that: "In the present state of knowledge it seems to us that acute disseminated encephalomyelitis is most likely a toxic reaction of the central nervous system occurring in a number of different virus conditions."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Titration of Scarlatinal Antitoxin by Means of a Skin Test in Chinchilla Rabbits.—Fraser and Plummer (*Brit. J. Exp. Path.*, 1930, **11**, 291) describes a method for the titration of scarlatinal antitoxin which is suitable at least for preliminary testing. Chinchilla rabbits were used and the skin tests were carried out just as in the human skin test. The test-dose of toxin used was eight to ten times that of the human test dose, and this was added to an equal quantity of the various dilutions of antitoxin. The tests were measured at the end of 24 and 48 hours after injection. In a series of carefully controlled experiments it was found that the accuracy of the skin titration in rabbits was within similar if not identical limits to that in human subjects, provided that one-half as many more animal tests are done. This necessity for a greater number of tests in rabbits was due to a greater dispersion in the readings. Two antitoxins could be distinguished if one were at least twice as strong as the other, and in 2 cases out of 3 this was possible if one toxin were only one and a half times as strong as the other.

Anatomical Characteristics of Tuberculosis in Jamaica.—Opie (*Am. Rev. Tuberc.*, 1930, **22**, 613) has reported upon 9 fatal cases of pulmonary tuberculosis in Jamaican adults, a large proportion of which had the characters of tuberculosis occurring in infancy and early childhood among people of European origin. Five cases were of this type, and in them the lesions had their origin in the lower lobes of the lungs, while the apices were either not involved or contained inconspicuous lesions. In 3 instances there was widespread tuberculous bronchopneumonia throughout the lungs with massive tuberculosis of tracheobronchial lymph nodes. In the fourth case the disease had made little progress in the lung, but there was massive tuberculosis of the tracheobronchial lymph nodes and death occurred from acute miliary tuberculosis. In the fifth instance the lesions in lung and lymph nodes were similar to those seen in the other 4, but there was also caseation of mesenteric lymph nodes. In all of these autopsies careful dissection failed to reveal any scars of preceding tuberculosis, and the lesions of lung and lymph nodes had all the characters of first infections. Of the remaining 4 cases the tuberculous lesions apparently had their origins in the apices of the lung, and in this respect resembled the tuberculosis of white adults. One case, however, was otherwise of childhood type, and was apparently a first infection. In 2 cases the lesions were intermediate between those typical of childhood and adult infections, while the last case showed a pulmonary tuberculosis similar to that usually seen in white adults.

Pulmonary Asbestosis. A Report of a Case and a Review.—Soper (*Am. Rev. Tuberc.*, 1930, **22**, 571) has reported a case clinically typical of pulmonary asbestosis. The patient had a history of exposure to asbestos dust for 12 years. The first symptoms of the disease appeared about 6 months prior to admission to hospital in the form of increasing dyspnea, malaise and loss of weight. He had a small amount of sputum, sometimes streaked with blood. Physical examination of the chest showed signs of bilateral pulmonary fibrosis. A few dry, crackling râles were heard at the bases about the whole circumference of the chest. These were also audible here and there over the whole chest. The outstanding feature of Roentgen ray plates of the chest was a diffuse fine type of shadowing, which, about the hilum of both lungs and about the bases, presented a "cobweb" appearance. Pathologic examination was not obtained in this case, but typically pleural adhesions are extensive, the lungs are firm and fibrotic, and the bronchi may be dilated with extensive peribronchial fibrosis. In addition, certain "golden yellow bodies," characteristic of the disease, may be expressed from the cut surface of the lung. These have been aptly called "asbestosis bodies." They may be shown to contain in their centers cores of asbestos fibers. Asbestos contains only a very small amount of free silica, but in the opinion of the author it probably conduces to a more rapid development of any concomitant tuberculosis, as in the better understood forms of silicosis.

Tuberculosis of the Liver.—Morris (*Am. Rev. Tuberc.*, 1930, **22**, 585) reports a case of tuberculosis of the liver in a man, aged 58 years, who had an advanced tuberculous lesion in the upper lobes of both

lungs with cavitation in the right upper lobe. Apart from the usual symptoms of terminal pulmonary tuberculosis, the patient presented more severe ones referable to the intestinal tract, all of which were attributed to intestinal tuberculosis. On physical examination the liver was slightly enlarged and tender on pressure. At autopsy the liver was found to be greatly enlarged with numerous large, hard, yellow nodular areas over the entire surface. These areas were filled with caseous material enclosed in fibrous capsules, varying from $\frac{1}{2}$ to 1 inch in diameter. Such cases of localized tuberculosis of the liver are rare and have never been diagnosed except by laparotomy. Miliary tuberculosis of the liver is found quite commonly in cases dying from pulmonary tuberculosis, but is quite uncommon without generalized tuberculosis. RANDOLPH (*Am. Rev. Tubere.*, 1930, **22**, 593) reports a case, however, in which there were no clinical signs of pulmonary tuberculosis, and Roentgen ray of the chest gave no suggestion of pulmonary lesion. The onset of the illness was acute with chills and fever and an irregular fever continued, ranging from 101° to 104° F. At the onset the liver was slightly enlarged, but increased in size from day to day, and from the ninth to the twelfth day with great rapidity. Fourteen days after the onset laparotomy was undertaken with a view to draining a possible abscess. The patient died on the following day. At autopsy the liver was found to be greatly enlarged with discrete scarring of the surface which proved to be due to a portal cirrhosis Numerous small, grayish-white nodules were scattered through the liver, and these were found on microscopic examination to be miliary tubercles of recent origin and all at about the same stage of development. Spleen and kidneys showed no tuberculosis. The explanation was offered that an old abdominal focus of tuberculosis had become active and seeded the liver through the portal circulation.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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An Unusually Mild Recurring Epidemic Simulating Food Infection.—SPENCER (*Pub. Health Rep.*, 1930, **45**, 2867) reports on the remarkable condition occurring periodically in the mountainous parts of the West, particularly in the National Parks. The onset is sudden and violent, with nausea, vomiting, sharp pains in the abdomen and diarrhea. In a few hours the attack was over and the patient well except for weak-

ness. The condition could not be associated with any particular item of food or water from any particular source. There was definite leukocytosis. Cultural studies and serologic tests gave no suggestive findings.

A Study of the Effect of Typhoid Vaccine When Given After Infection.—CROUCH (*U. S. Pub. Health Rep.*, 1930, **45**, 2429) presents data which would seem to justify the tentative conclusion that typhoid vaccine is well worth while when given after the infection is received, provided the first dose is given before the onset of symptoms and provided further that three doses are given. Typhoid vaccine when given soon after the onset of symptoms is of little or no benefit.

Mottled Enamel in a Segregated Population.—KEMPF and MCKAY (*U. S. Pub. Health Rep.*, 1930, **45**, 2923) review the history of this condition of the teeth and emphasize the high frequency of the discoloration in areas where it prevails. Cuts illustrate the disfiguring nature of the condition. Permanent teeth alone are involved. The condition in the community under study coincided with the introduction of deep well water. The data point to rather exact localization of mottled teeth and proved a relation to the water supply, but the exact fault of the water has not been determined.

The Typhus-Rocky Mountain Spotted Fever Group. An Epidemiological and Clinical Study in the Eastern and Southeastern States.—RUMREICH, DYER and BADGER (*Pub. Health Rep.*, 1931, **46**, 470) have separated certain eruptive diseases occurring in the eastern seaboard states into two clinical entities; one of these is endemic typhus of the type previously described by Brill, Maxcy, and others, the other a virus infection of the Rocky Mountain spotted fever type. There is an important difference between the two in that the latter group of cases have a definite mortality somewhere in the neighborhood of 20 per cent, whereas the typhus cases are practically without fatalities. The onset is very similar in the two, but the duration of the fever in the typhus cases is apt to be cut short by a crisis on the fourteenth or fifteenth day, while it may be either shorter or longer in the spotted fever group of cases. The distribution of rash is also different, in the typhus cases beginning on the thorax and abdomen, spreading later to the arms and legs and rarely involving the face, whereas in the spotted fever group of cases the extremities are involved first and the face usually is implicated. The seasonal distribution is substantially similar and there is a strong suggestion on epidemiological grounds that the Rocky Mountain spotted fever cases are tick-borne, while the suggestion, perhaps not quite so strong, is that the typhus cases might have been infected from fleas.

Undulant Fever. With Special Reference to a Study of Brucella Infection in Iowa.—HARDY and his associates (*U. S. Pub. Health Rep.*, 1930, **45**, 2433, 2525) discuss the subject at length. The epidemiologic part of their studies is summarized as follows: Undulant fever due to

infection with the abortus or suis varieties of Br. melitensis is wide spread, and in regions in which systematic investigations have been conducted the disease has been found to be of not infrequent occurrence. It has involved chiefly young and middle-aged adults, and males have predominated in all but very few studies. Men on the farms and packing-house employees have been particularly involved. Cattle have been generally regarded as the source of human infection, but in some localities hogs have played an important part. That direct contact with animals often accounts for human infection is being more generally recognized. Evidence indicates that the skin may be an important portal of entry. Otero, of Porto Rico, in a personal communication, writes as follows concerning his experiments on human volunteers: "It may be of interest to know that some of our inoculations, through abraded skin have been successful, giving rise to clear-cut cases of undulant fever after a single inoculation, in some cases with strains that were fed repeatedly with apparently no symptoms. I have 6 such cases at present running fever." The authors feel that the date presented make untenable the opinion that the ingestion of raw dairy products from infected cows is the only means of transmission of undulant fever. It is apparent, in Iowa, at least, that approximately one-half of the cases result from a second means of transmission, namely, through contact with infected animals, their tissues, or discharges; the infection in all probability entering through the skin. The section on Prevention deserves special attention. The important parts may be summarized as follows: Vaccination with killed cultures is valueless. Proper pasteurization of milk renders the fluid safe. The agglutination test is recommended to be applied to cattle to enable the owners to eliminate infected animals. The ultimate control of the condition lies with the veterinary profession.

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